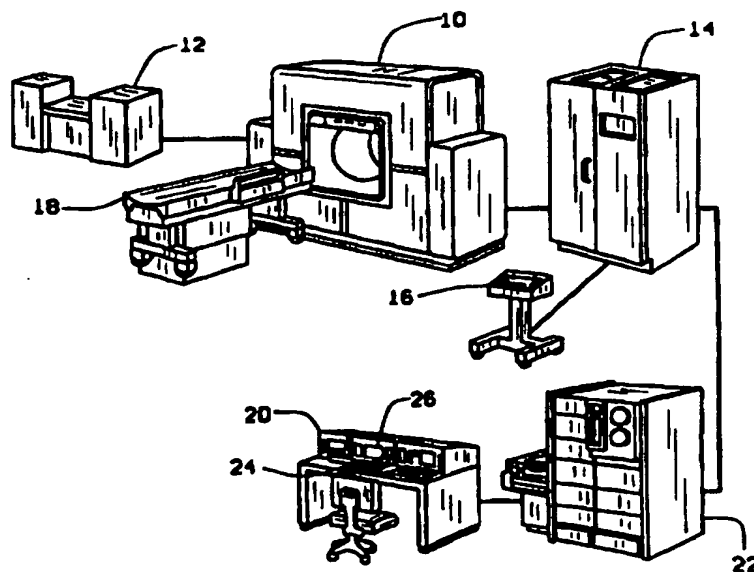


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(54) Title: **PREDICTING CT CONTRAST ENHANCEMENT WITH FEEDBACK**

(57) Abstract

A method and apparatus for predicting optimum injection protocol for a contrast agent by analyzing the predicted enhancement levels based on a mathematical model of human cardiovascular physiology of a specific body habitus and updating the injection protocol until acceptable enhancement levels are predicted, determining an optimum scan interval, and controlling a CT scanner (10) and contrast agent injector.

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Predicting CT Contrast Enhancement With Feedback

Field of the Invention

This invention relates generally to an apparatus and method for predicting organ specific contrast enhancement prior to computed tomography scanning of a patient. Specifically, this invention relates to a
5 computer simulation of contrast agent transport throughout the body to predict organ specific enhancement in patients of variable height and weight subjected to various contrast injection protocols to enable operator selection of an appropriate injection protocol prior to
10 commencing the scan and to use measurements of actual contrast agent transport throughout the body after injection as feedback to verify and calibrate the predictions.

Background of the Invention

15 Computed tomography (CT) is a widespread diagnostic imaging method which measures the x-ray attenuation coefficient of matter. This x-ray attenuation coefficient is depicted in terms of
5 Hounsfield Units (HU). During a CT scan, a collimated X-ray beam is directed on the patient and the attenuated remnant radiation is measured by a detector whose response is transmitted to a computer. The computer considers the location of the patient and the spatial
10 relationship of the x-ray beam to the region of interest. The computer analyzes the signal from the detector so that a visual image can be reconstructed and displayed on a monitor. The image can then be viewed or stored for later evaluation.

15 Hounsfield Units reflect the relative absorption of CT x-rays by matter, the absorption being related to the atomic number, electron density, physical thickness of that matter, and the energy spectrum of the x-rays. Because of the similarity in electron density of various

tissues in the body, CT scans sometimes result in poor imaging. In an attempt to obtain better results in such circumstances, a contrast agent, such as iodine, can be injected in the patient's blood stream to change the
5 relative radio-density of the tissues, and improve overall diagnostic efficacy.

When using a contrast agent, it is extremely important to coordinate the time of the scan with the time of greatest levels of contrast in the region of
10 interest, in some instances with respect to a threshold value. Because the contrast agent is injected into the blood stream, many physiological factors can affect the start time and duration of a sufficient level of contrast in the region of interest. For example, because the
15 cardiovascular system provides the means for circulation of contrast agent throughout the body after it is injected into the blood stream, a patient's cardiac output can have a significant effect on the distribution of the contrast agent as well as the time taken for the
20 contrast agent to reach a particular organ or vessel.

Current understanding of intravenous contrast enhancement is further complicated by multiple interacting factors including contrast agent type, volume and concentration, injection technique, catheter size and
25 site, scanning technique, patient characteristics and tissue characteristics. Of these factors, all of which have influence on contrast enhancement, the variables which cannot be controlled are those related to the patient. These include age, gender, weight, height,
30 cardiovascular status, renal function and other disease status. In the past ten years, many clinical studies testing various intravascular contrast agent and injection protocols have been reported. However, in many respects, contrast enhancement still relies heavily on
35 the experience and intuition of the physician rather than

rigorous, quantitative analysis of the mechanism of contrast enhancement.

Summary of the Invention

The present invention provides a method of and an apparatus for predicting tissue specific CT contrast enhancement in a patient with a specific body habitus subjected to different contrast injection protocols. The method is preferably implemented in a computer program, and the computer itself may be used to also control the CT scan in accordance with an operator's choice. Such a physiological model of contrast enhancement has many potential clinical applications.

10 The present invention utilizes a compartmental model of the human cardiovascular system and assigns differential equations describing mass transport to each compartment of the model. Regional circulation parameters such as blood volume, regional blood flow and
15 extracellular fluid volume were estimated using available data to provide input to the equations. Local tissue structures such as organs and vessels were modeled mathematically to describe the distribution and dispersion of an intravascularly-administrated contrast
20 agent. A global model was then formed by integrating the regional circulation parameters with the models of local tissue structures.

The present invention, which is preferably implemented in a computer program, allows an accurate
25 prediction of the time varying distribution and concentration of contrast in the body. This in turn allows an operator to predict the time and duration of maximum enhancement in a specific organ or tissue in a patient for a particular injection protocol. Most
30 importantly, the operator can use the present invention to predict the time a scan should be started and the duration of the scan based on output data from the program. This output can take the form of a data stream

or can be a graph of contrast enhancement, versus time. With more advanced generations of CT machines, such as spiral and helical CT scanners as are known in the art, a typical scanning procedure can be completed within

5 approximately 30 seconds. The present invention enables an operator to choose an injection protocol to ensure that the entire scan takes place during a period of maximum enhancement, and while enhancement exceeds a suitable threshold.

10 In the prior art, there are devices which monitor and output contrast enhancement levels for a region of interest. Using these prior art devices, an operator injects the contrast agent into the patient, views the output, and determines when to begin a scan based on when
15 the enhancement level attained in the patient's region of interest becomes acceptable. The prior art devices require the injection of the contrast agent and low dose x-rays of the region of interest. For example, in the prior art, the injection of a contrast agent is started
20 and the prior art device monitors at regular intervals the enhancement level in the region of interest and provides an output. The operator can view the output and then decide when to begin the scan.

Prior art techniques to determine the enhancement
25 level in an organ include low dose pre-scanning of the organ during injection of the contrast. One such example is U.S. Patent No. 5,459,769 to Brown. In Brown, after a short delay upon initiating the injection, low-dose x-rays are taken of the organ to be scanned. Images are
30 constructed from the low-dose x-rays and the images are displayed for the operator to determine when the enhancement level in the organ is sufficient to begin a full dose scan.

The present invention is a significant improvement
35 over the prior art in that it allows prediction of contrast enhancement levels and duration of those

enhancement levels prior to injection of the contrast agent and without the need of low dose x-rays. Moreover, because different injection variables, such as rate and concentration, can alter the enhancement levels, the present invention allows calculation of various alternatives to choose the best injection scheme for a particular patient. The prior art devices do not assist the operator in determining whether a particular patient having a specific body habitus will even acquire a desired threshold level of enhancement with a given injection protocol.

Therefore, if the threshold level of enhancement is never reached because of the patient's specific body habitus or an improper injection protocol for the particular patient, a scan cannot be completed and the entire process must be repeated, including a second injection. Even then, the operator cannot be certain that the revised injection will ever reach a desired threshold level of enhancement based on that patient's specific body habitus and injection protocol, nor whether the threshold level, if attained, will be maintained during the entirety of a desired scan duration. This is particularly important for scans of certain tissues whose contrast enhancement behavior is complex, as explained in greater detail below.

The present invention also allows an operator to adjust the collimation or slice thickness and CT table speed to optimize a scan. During a CT scan, a patient lies on a table which moves through the CT scanner from head to toe vertically, and over the selected region of interest. The collimation or slice thickness is the thickness of the slice of the patient's body that is transaxially scanned. The table can usually be moved at a rate per second of up to two times the collimation thickness. Using the method and apparatus of the present invention, an operator can optimize the collimation rate

and table speed. For example, if there is a limited period of threshold enhancement, the operator knows that an increased table speed or an increased collimation thickness must be used to ensure that the entire scan is
5 completed during the time period of maximum enhancement. Customizing the scan is less precise with the prior art.

In the present invention, the computer program allows an operator to determine how long the predicted enhancement level exceeds the threshold enhancement.
10 That information provides the operator with a means to adjust various scan parameters such as scan duration, scan start time and table speed, to be certain that the scan takes place during a period when the predicted enhancement is above a threshold enhancement. Thus, the
15 invention was a significant improvement over the prior art.

Building on the invention as described above, the inventors herein have improved it by providing for a method of using the predicted enhancement levels to
20 optimize injection protocol and adjust the injection parameters to increase or decrease the time that the predicted enhancement level exceeds the threshold. The inventors have also improved it by providing a means for determining the optimum scan start time when the
25 predicted enhancement level exceeds the threshold for a period much greater than the scan duration.

The present invention can be implemented in many ways including a separate computer or integrated with the computer of a CT machine. All that is required is a
30 computer having the invention programmed therein integrated with the controls of the machine. The present invention can also be implemented in a contrast injector system which is equipped with a computer for predicting contrast enhancement for given inputs of patient
35 parameters and contrast injection protocol. In this way,

adjustments to the injection protocol are readily made using the injector.

The contrast injector having a computer with the invention programmed therein can be operated as a fully integrated system with a CT scanner or as an independent system. When the present invention is used as a part of a computer system integrated with both an injector system and a CT scanner equipped with low-dose pre-scan CT, the optimal set of scan parameters can be adjusted based on actual enhancement measurements acquired with low-dose scanning.

The present invention is capable of using standard values for variables which influence enhancement levels and also allow input of patient specific values. For example, a particular patient habitus may be such that the standard values for variables such as blood volume, blood flow etc., will not provide an accurate prediction of enhancement levels. The invention utilizes several methods to resolve such situations. One method provides for the input of patient specific information to customize the operation to the particular patient. This includes patient specific variables such as weight, age, height and gender. These variables can be measured and input to adjust the standard variables accordingly.

On occasion, other variables which are not readily measurable may need to be modified. As is well known in the art, cardiac output cannot be measured as readily as height or weight. Of course, a patient with a known history of heart failure or increased age will most certainly have a cardiac output below normal. If this is the case, the invention of the parent allows adjustment of the standard variables accordingly.

Another aspect of the method allows the operator to choose several alternative values for cardiac output and generate a family of predicted enhancement curves for each value. After injection of contrast agent is

started, actual measurements of enhancement can be compared to the initial portions of the family of curves to determine which family member most closely resembles the actual results. In this way, early in the scan and
5 before the threshold has been reached, a choice of which curve to utilize to best predict when the scan should occur can be made. This choice can be made by the operator or automatically by the computer.

The inventors herein have improved upon this
10 method by using predicted aortic enhancement levels compared with sequential measurement of actual aortic enhancement levels using low-dose pre-scanning as an indicator of unknown patient specific parameters such as the cardiac output of the patient.

15 In the present invention, the predicted enhancement levels are computed for a given set of patient specific parameters in an injection protocol. Prior to any injection of the contrast into the patient, the operator enters the patient specific parameters and
20 the injection protocol into the computer which can be integral with an injector, a CT scanner or be a stand-alone personal computer. The method of the present invention provides an output from the computer which gives the predicted tissue enhancement level of the
25 tissue to be scanned as a function of time. Based on that output, the operator uses the present invention to modify the injection protocol in order to ensure that the predicted tissue enhancement function exceeds a threshold level for at least as long as the desired scan duration.

30 If the predicted tissue enhancement function is shown by the output to be substantially greater than the threshold level, the present invention allows the operator to modify the injection protocol to decrease the volume or flow rate. If the predicted enhancement
35 function does not meet or exceed the threshold level or does not exceed the threshold level for the length of the

scan duration, the present invention allows modification of the injection protocol by increasing the flow rate or volume of contrast. The program iterates to again compute and provide a revised predicted tissue
5 enhancement function output based on the revised injection and/or rate.

If the predicted tissue enhancement function is known to be above the threshold level for a period of time substantially greater than the desired scan
10 duration, the operator can use the method above to decrease the injection rate or volume of contrast or both to reduce the predicted enhancement level to a range which still satisfies the scan parameters, thereby saving contrast agent and minimizing any potential side effects
15 to the patient. In the alternative the method provides for prediction of the optimal temporal window for performing the scan within the period that the enhancement exceeds the threshold.

After the operator is satisfied that the injection
20 protocol chosen and the patient specific parameters will produce an acceptable enhancement level as shown by the output of the present invention, the operator can further increase the accuracy of the prediction by predicting and low-dose monitoring enhancement in a region of interest
25 and comparing the prediction with the actual measurement from the monitoring to update or revise the predicted tissue enhancement function. In this way, the invention uses feedback from actual enhancement measurements to fine tune the predictions.

30 To practice this aspect of the invention, the operator performs a base line scan over a distinct region of interest. The base line scan is a low-dose or partial scan in which the x-ray dosage is reduced substantially less than a typical scan. After completing the base line
35 scan, the operator begins the injection of the contrast agent. After initiating the injection, the operator

performs low-dose pre-scan of the region of interest, such as the aorta, to obtain actual aortic enhancement levels. The pre-scan is virtually identical to the base line scan described above and is also a low-dose scan and
5 can use less than a full revolution of the gantry of a CT scanner. Using the actual measurement of enhancement in the aorta, the present invention can calibrate the model for patient parameters such as cardiac output and provide revised tissue enhancement predictions.

10 The present invention has particular application where the organ or vessel being scanned is incapable of maintaining threshold enhancement levels for a sustained period. One such example is CT angiography. In CT angiography, a CT scan is taken of a blood vessel or
15 vessels. Unlike organs, blood vessels do not maintain high enhancement levels over time and the timing of the scan is critical. CT angiography is performed in the prior art by injecting a test dose of contrast agent and measuring with low dose x-rays the elapsed time for the
20 contrast agent to reach the region of interest. Thereafter, a full dose of contrast agent is injected and a scan is initiated after lapse of the previously measured time delay. However, there is no guarantee of a particular enhancement level being attained or sustained
25 as required to achieve a successful scan. Using the invention comprising the method and apparatus disclosed herein, one can more accurately predict not only the time delay, but also the degree of enhancement and its duration.

30 While the principal advantages and features of the invention have been described above, a greater understanding of the invention may be attained by referring to the drawings and the description of the preferred embodiment which follow.

Brief Description of the Drawings

Figure 1 is a diagram showing the components of a complete CT scanner system and a computer control console;

Figure 2 is a schematic diagram of the major organs of a human cardiovascular circulation system;

Figure 3(a) is a block diagram of a single well stirred compartment with an input having a constant input concentration C_i and input flow rate Q_i , the compartment having a volume V and an output with a concentration C_o and an output flow rate Q_o ;

Figure 3(b) is a graph of the input concentration of the input in Figure 3(a) and a graph of the corresponding output concentration C_o over time;

Figure 4(a) is a block diagram of an organ modeled in three spaces: intravascular (IV), extracellular (EC), and intracellular (IC);

Figure 4(b) is a block diagram of the IV and EC spaces of Figure 4(a) detailing the mass transfer rate (dM/dt) therebetween;

Figure 5 is a block diagram of the global cardiovascular model of the body;

Figure 6 is a flow chart showing the method steps for determining predicted contrast enhancement level;

Figure 7 is a flow chart of a subroutine of the method of Figure 6 for operator designation of patient information and contrast protocol information;

Figure 8 is a flow chart of a subroutine of the method of Figure 6 which assigns a differential equation to each element of the cardiovascular model;

Figure 9 is a graph showing the linear relationship between enhancement in Hounsfield Units (H.U.) and concentration of Iodine (I mg/ml);

Figure 10 is a graph showing simulated (10b) and empiric (10a) aortic and hepatic enhancement using the biphasic-low flow rate injection protocol given in Table 6;

Figure 11 is a pair of graphs showing simulated (11b) and empiric (11a) aortic and hepatic enhancement using the uniphasic-low flow rate injection protocol given in Table 6;

5 Figure 12 is a graph showing simulated (12b) and empiric (12a) aortic and hepatic enhancement using the uniphasic-high flow rate injection protocol given in Table 6;

10 Figure 13 is a graph showing simulated aortic and hepatic enhancement curves generated by the invention for hypothetical patients weighing 110, 150, 200 and 250 pounds;

15 Figure 14 is a graph showing simulated aortic (14a) and hepatic (14b) enhancement curves for permeability (PS) values of .1, 1.0, 20 and infinity;

20 Figure 15 is a data stream output generated by the invention showing predicted aortic and hepatic enhancement levels in a hypothetical patient with standard blood volume and standard cardiac output using uniphasic-high flow rate injection protocol in Table Six;

 Figure 16 is a graph output generated by the invention showing predicted aortic and hepatic enhancement levels versus time using the data in Figure 15;

25 Figure 17 is a drawing of a power injector system with its various components;

 Figure 18 is a graph output generated by the present invention showing the predicted enhancement function versus time superimposed over a line representing a threshold enhancement level;

30 Figure 19 is a graph output generated by the present invention showing the predicted enhancement function and identifying those intervals for which the predicted enhancement function exceeds the threshold value;

Figure 20 is a table showing an output of the present invention using the process steps in the flow chart of Figure 21;

Figure 21 is a flow chart showing the method steps of the present invention used to calculate an injection flow rate and volume which provide a predicted enhancement function which exceeds a threshold value for a period greater than the scan duration and the method steps to select an optimum scan interval within the period;

Figures 22A and 22B are graphs generated using the present invention showing four predicted aortic enhancement curves 22A and four different predicted hepatic enhancement curves 22B corresponding to four alternative cardiac outputs;

Figure 23 is a graph showing predicted and actual aortic enhancement along with predicted and actual hepatic enhancement for a given patient;

Figure 24 is a table generated using the present invention showing four predicted aortic enhancement levels for four alternative cardiac outputs and the actual predicted enhancement levels at specified elapsed times after injection with the corresponding area under the enhancement curve (AUC) calculations;

Figure 25 is a table generated using the present invention showing predicted hepatic enhancement levels at specified elapsed times after injection using the cardiac output calculated from the table of Figure 24; and

Figure 26 is a flow chart showing the method steps of the present invention to select the optimum onset of hepatic scanning from a table of predicted optimum onset times correlated to actual measured times for the actual enhancement curve to achieve an AUC of a predetermined amount.

Detailed Description of the Preferred Embodiment

Computed Tomographic (CT) scanning is an invaluable radiologic diagnostic tool. The major components of a conventional CT scanner are shown in Figure 1. The CT scanner 10 contains the x-ray tube and 5 detector array. Power is supplied by a high voltage generator 12 controlled by scanner electronics 14 and scanner service module 16. The patient support and positioning couch 18 is moveable to transport the patient through the scanner 10. The scanner 10 and voltage 10 generator 12 receive electronic commands from the operating console 20 and transmit data to the computer system 22 for image production and analysis. The operating console 20 usually contains an interactive keyboard 24 and CRT monitor 26.

15 Many radiographic procedures, including CT scans, require an injection of contrast medium under specific control conditions. For example, CT scanning requires a high degree of control over the injection of the contrast agent and the parameters of the injection protocol in 20 order to maximize the accuracy of the scan. It would be difficult to consistently perform these injections by hand. Therefore, these injections are usually performed with a mechanical-type device known in the art as power injectors or injector systems. Injector systems allow 25 significant control of the injection of contrast into a patient prior to a CT scan.

Injection systems for CT scans have several basic components. An example of an injector system is shown generally as 128 in Figure 17. The injector system 30 includes a control unit 130, mounted on a pedestal 132, an injector head 134 and arm 136 integral to the unit. The entire injector system 128 can be wheeled about as a unit for use with the CT scan machine as shown in Figure 1. The control unit of the injector comprises a control 35 panel for setting up the injection and a display for displaying instructions and data. The controls and

indicators present on the control panel will vary with the type of options available on the system. One example of an injector system is the Mark V Plus injection system manufactured by Medrad of Pittsburgh, Pennsylvania.

5 The injector head accommodates a syringe and provides for power injecting. The arm connects the head to the console permitting easy movement for loading or injecting. The height allows placement of the head over the patient during a CT scan. In the alternative, the
10 injector head and arm can be mounted to the CT scan table, or overhead from a ceiling mount, or wall mounted near a CT system with the control panel being located on a console integrated with the controls of the CT scan.

 The injector head can be either floor mounted or
15 track mounted on an overhead system. In most cases, the control panel is mounted inside the CT scan control booth for operator safety. Most injector systems also contain a microprocessor and memory for storing computer programs which can be recalled when needed. A warming system may
20 also be included in an injector system which warms and maintains the contrast medium at or near body temperature. This will help reduce viscosity of contrast medium, resulting in a decrease in resistance of contrast medium flow and decrease in a patient discomfort
25 experienced during injection. Most injector systems use a power high pressure mechanism, such as an electric drive motor coupled to a jack screw, to drive the piston in or out of the syringe and deliver the contrast.

 Injector systems can also be interfaced with a CT
30 imaging system. This interfacing of an injector to a CT imaging system allows variations such as causing the injector to be triggered by the imaging system or causing the imaging system to be triggered by the injector. Bi-directional controls are also available to allow either
35 device to control the other and allow an operator to choose how to sequence and time the devices when they are

connected. For example, the CT scan imaging system can have a control which allows it to trigger the injector and the injector can have a control which allows the injector to send a signal to the CT imaging system to
5 trigger the start of a scan. The details of interfacing the injector system with an imaging system and the controls available are well-known in the art.

The control panel on an injector system is used to set the parameters of the injection sequence. It usually
10 consists of an alpha-numeric keyboard and buttons for various input parameters as well as several display windows including a window for displaying system messages. The control panel accepts and displays injection parameters, displays injection results and
15 other messages related to the control of the injector system. The control panel allows the operator to program the injector system to control various parameters of the injection process including the flow rate, volume, injection duration, injection pressure, and injection
20 delay. The flow rate is defined as the delivery rate of the contrast (amount delivered per unit of time). The flow rate is dependent on the viscosity of the contrast agent, the length and diameter of the catheter, and the injection pressure. The particular flow rate chosen for
25 a specific procedure is governed by the procedure itself, the vessel entered and the patient habitus. Flow rates can vary from as low as .1 ml/s to as high as 40 ml/s, depending on these factors.

The present invention is preferably implemented in
30 a computer program. Because most CT scanners and injector systems utilize computers to control their operation, the present invention could be easily integrated therewith. In that fashion, the operator could run the program prior to the injection or prior to
35 the scan and the computer can determine the optimum injection and scan parameters and using the determined

values complete the injection and the scan accordingly. In this way, the injection system computer or the CT scan computer (or the shared computer on a combined system) can determine as well as implement the injection protocol and the scan parameters. In the alternative, a separate computer which contains the program could be utilized. The scan parameters and injection protocol could be determined by running the program in the separate computer and then input into the injector system computer or CT scan computer by the operator or through computer data transfer methods.

The invention utilizes a model of the human cardiovascular system to describe mass transport of contrast agent throughout the body. The cardiovascular system provides the means for circulation of contrast agent throughout the body after it is injected into the bloodstream. The human cardiovascular system is very complex and has numerous controlling mechanisms, including neuronal, hormonal and psychological controls. A simplified human cardiovascular system as shown schematically in Figure 2 consists of the heart, vascular networks, and key organs which serve as reservoirs. Normal blood volume and flow distribution throughout the body are well established in the prior art and are given in the Tables 1 and 2 (All Tables are shown in Exhibit A attached hereto and incorporated herein by reference).

Based on well known information, the model assumed that the average blood volume was 5 liters. This includes 3 liters of plasma and 2 liters of red blood cells. The average cardiac output was also estimated from known sources to be 6.5 liters per minute. These values were used to describe a standard model of the cardiovascular system. However, the method and apparatus of the invention allow these values to be adjusted according to the patient's age, gender, weight and height using standard nomograms outlined below.

Because contrast agent diffuses passively from the bloodstream across the capillary membrane into the extravascular space, the distribution of fluid throughout the body was included in the cardiovascular model. The
5 amount of total body water (TBW) in an adult of average weight (70 Kg) was assumed to be 40L. TBW was divided into two major components, intracellular fluid (ICF) and extracellular fluid (ECF). The ECF was further divided into several smaller compartments including interstitial
10 fluid, plasma, and cerebrospinal fluid. The interstitial fluid is the largest compartment and lies in the lymphatics and the spaces between cells.

The ECF volume is usually estimated with dilution methods in which a substance is injected into the blood
15 stream and diffuses throughout the entire extracellular fluid compartment with little entering into the cells. However, an ideal substance for such dilution studies has not been identified, and measurements for a 70kg adult have ranged from 9L to 22L depending on the substances
20 used. The size of the measured ECF decreases with increases in the molecular weight of the substance used. The apparent volume distribution of iohexol has been reported to be .27 l/kg. Thus, for a 70Kg adult, this equates to an ECF of 18.9L. In the model this value for
25 ECF volume was used which includes a plasma volume of 3.0L. The overall estimated distribution of body fluid used in the cardiovascular model is summarized in Table 3.

The detailed distribution of fluid in a local
30 organ was estimated from the standard mass of an organ and its water content. The volume of the total systemic capillary bed is estimated to be about 300 ml. However, a detailed breakdown of capillary volumes in different regions is not available. In addition, the number of
35 capillaries within an organ varies considerably from one organ to another. It is believed that the regional

capillary volume is directly proportional to a regional blood flow and the cardiovascular model applied this assumption. These values are likely overestimated in highly perfused organs such as the kidney and the liver but this did not hinder the performance of the model. Table 4 shows the regional capillary volumes in the systemic circulation estimated from the regional blood flow values given in Table 2.

A calculation of the regional distribution of the extracellular and intracellular fluid was also necessary for the invention. The regional distribution of total body fluid can be calculated from the known mass of each organ and its water content, assuming a density of 1.0 g/Ml. The weight and percent of water content of the visceral organs are shown in Table 5 along with their total fluid value minus the capillary volume. Without available information, the model assumes 70% water content in the stomach, spleen and intestine. The lung consists of 50% parenchyma and 50% non-parenchyma tissues whose capillary volumes are 150 ml and 5 ml, respectively.

The total body fluid of the upper extremities, trunk, and lower extremities was calculated by subtracting from the total body water volume (40L), the blood volume (5L), and the total fluid of the visceral organs minus the capillaries (4,726 mL). The mass ratio of the lower extremities and trunk to the upper extremities is about 4:1. Thus, the total body fluid of the upper extremities becomes 6,055 mL and that of the lower extremities and trunk, 24,219 mL.

Table 3 shows the overall volumes of ICF fluid and ECF fluid as 19.1L and 15.9 L. respectively. However, regional distribution of the ICF and ECF is not shown. Some tissues such as the skin, adipose tissue, G-I tract, and liver have larger extracellular to intracellular fluid ratios than, for example, muscle. As no data

regarding such fluid ratios are available, it was assumed the ratio of ECF to ICF to be the same in all body regions. For example, the ECF and ICF volumes of the liver were estimated as 524 and 629 mL respectively.

5 After regional blood flow, blood volume, and distribution of body fluid were estimated, local structures were modeled mathematically to describe the distribution and dispersion of intravascularly administered iodinated contrast agent within local
10 regions. The blood vessels are viscoelastic with complex mechanical properties to accommodate pulsatile blood flow and various pressure gradients. Although the blood flow in large vessels is generally streamlined, some mixing occurs within the blood vessel because of molecular
15 diffusion, flow pulsability and convections at multiple branching points. The dispersion may be even greater in smaller and low pressure vessels. To simplify the model, blood vessels were represented as rigid structures without directly incorporating their dynamic pulsatile
20 properties in the.

 A blood vessel could be analyzed in the cardiovascular model as a simple conduit without any longitudinal mixing. This is known in the art as "plug flow." In this type of model, each artery and vein is
25 divided into segments, and blood enters as plugs for each heartbeat and displaces an equal volume of blood without any longitudinal mixing. The major problem with this approach is excessive demands on computer memory required to store the history of each segment throughout the
30 circulation. An alternative approach is to consider a blood vessel as a well-stirred compartment or well-mixed pool of blood. This approach simplifies computation, requires far less computer storage and has been shown to perform as well as the plug flow model in the prior art.
35 Thus, in the cardiovascular model, the heart and blood vessels were analyzed as well-stirred compartments.

A single, well-stirred compartment contains a constant volume, V , with a single inlet flow and a single outlet flow as shown in Fig. 3(a). Q_i and Q_o represent the input and output volumetric flow rates of the blood, respectively. The input and output flow rates are the same in a constant volume compartment ($Q=Q_i=Q_o$). C_i and C_o represent the input and output concentrations of contrast agent, respectively. Since we assume the compartment to be well mixed, the concentration within the compartment is the same as that of the output. A mass balance of the concentration is described by Fick's Principle, shown schematically in Figures 3(a) and 3(b) in the following equation:

$$V \cdot dC_o/dt = Q(C_i - C_o).$$

For a given volume, V , a given volumetric flow rate Q , and a given input concentration, C_i , we can estimate the output concentration, C_o , by solving this differential equation. The net effect of a well mixed compartment is to disperse the input concentration over the compartment resulting in more broadly distributed output concentration over time. For constant flow rate, Q over a fixed time interval, T , the input concentration given as a step function is mathematically transformed to the output concentration curve as shown in Fig. 3(b). The transformation is described mathematically as two exponential functions of V , Q and T . The output concentration curve is broader temporally than the input concentration curve, and a central peak is present.

Modeling an organ is more complex than modeling a blood vessel because the contrast agent is no longer confined in the intravascular space and permeates through the capillary membrane into the extravascular space. The simplest approach to modeling an organ is to assume that it also is a well-stirred compartment. However, the single compartment organ model does not address differences in the exchange of contrast agent along

subcompartments within an organ and is limited in describing the behavior of substances with different transcapillary permeabilities. A common alternative approach used in the prior art to investigate the distribution of chemotherapeutic agents throughout the body involves splitting each organ into three well known spaces: the capillary or intravascular space (IV), the extracellular space (EC), and the intracellular space (IC). This is shown schematically in Fig. 4(a). For a given organ, each of these three spaces was modeled as a single, well-mixed compartment. Diffusion through membranes, either active or passive, permits exchange of substances along the spaces within the organ. However, because iodinated contrast agent does not penetrate into the cells, only the intravascular (IV) and extracellular (EC) compartments were considered and the intracellular (IC) compartment was ignored.

Transcapillary exchange of substances between the intravascular and extracellular compartments can be described by Fick's Law of Diffusion and is shown schematically in Figures 4(a) and 4(b). The mass transfer rate (dM/dt) is proportional to the diffusion coefficient (D), the surface area (S), and the concentration difference ($C_i - C_o$) for a given membrane thickness (dx) as represented by the following equation:

$$dM/dt = DS(C_i - C_o)/dx.$$

For a thin membrane, the mass transfer rate is simpler such that permeability (P) is commonly used to combine D and dx as a unit resulting in the following equation:

$$dM/dt = PS(C_i - C_o)$$

To complete the mathematical model, two governing differential equations were applied to each organ. One for the intravascular space and the other for the extracellular space. The intravascular space had two transport components. The first component was obtained from blood flow related mass balance, i.e., the inflow of

contrast agent minus the outflow. The second component was obtained from the mass balance related to the transcapillary exchange within the extracellular space. For the extracellular space, only one transport component was considered: the mass balance related to transcapillary exchange with the intravascular space. These equations are as follows:

$$V_{iv} * dC_{iv} / dt = q(C_i - C_{iv}) - PS(C_{iv} - C_{ec})$$

$$V_{ec} * dC_{ec} / dt = PS(C_{iv} - C_{ec})$$

- 10 The global model, shown schematically in Figure 5, was formed by integrating the regional circulation parameters with the models of local regions. In the model, contrast agent was assumed to be injected through an antecubital vein, mixed in the right heart,
- 15 distributed throughout the body and excreted by the kidneys according to the glomerular filtration rate.

The residence time of contrast agent in an organ was estimated by the time duration of the contrast agent in the capillaries and ECF spaces. The residence time depends on the size of these spaces as well as the transcapillary exchange rate. When a substance is confined to a blood vessel, the circulation time is measured by injecting rapidly a dye or radioactive tracer into a peripheral vein and detecting the moment when it arrives at a sampling site. The volume of a blood vessel travelled by a substance is calculated by multiplying the volumetric flow rate and the circulation time. The mean circulation time from the antecubital vein to the right atrium is approximately 6.9 seconds in an average adult.

25 The time can range from 3 to 14 seconds. This is the temporal difference between the antecubital and the right atrial injections.

Intravascular contrast agents are eliminated from the body mainly by the kidneys. The process is rapid with approximately 50% of injected contrast agent being excreted within two hours presuming normal renal

35

function. The total excretion rate of contrast agent is obtained by multiplying the plasma concentration with a glomerular filtration rate, usually about 19% of renal plasma flow. Peak renal excretion is closely related to
5 peak plasma concentration, because renal plasma flow is relatively constant.

Regional blood flow is expressed according to the magnitude and direction of the flow. For example, the cardiac output is 6500 mL/min., directed away from the
10 right heart. In Figure 5, the right and left heart are represented by boxes by denoting well stirred compartments. Each blood vessel is represented by a circle surrounding a number which represents its volume in milliliters. Large blood vessels are further divided
15 into multiple smaller compartments in series, typically 20 mL for arteries, and 100 mL for veins: the volume of systemic veins is about 4 to 5 times that of associated arteries. This division scheme in large vessels is rather arbitrary and was based on computational
20 convenience. However, the total blood volume in a given blood vessel closely followed known physiological values.

In Figure 5, each organ is shown as a box split into two sub-compartments, the upper number denoting intravascular (capillary) volume and the lower number
25 denoting extracellular fluid volume. The concentration of contrast agent in an organ is determined by the ratio of the total mass to the total volume of contrast agent within that organ. The total mass of contrast agent within an organ is calculated by summing the products of
30 the concentrations and the volume in the intravascular and extracellular spaces. The organ volume is obtained by adding the intravascular (IV), extracellular (EC) and intracellular (IC) volumes.

A total of 104 ordinary differential equations
35 were used to describe the cardiovascular model. These equations were solved using the numerical integration

programs of the fifth order Runge-Kutta method on a personal computer. Using a power Macintosh or IBM PC the computation took a few seconds to compute. The contrast concentration curve over time was calculated for each region by solving differential equations of the model for a given contrast injection protocol and a hypothetical patient with variable weight, height, gender and age.

Referring to Figure 6, the method is shown as a flow chart. The first step in the method is to call the patient/contrast information subroutine shown in Figure 7. This subroutine accepts operator input of patient and contrast information which will affect physiological parameters of contrast enhancement. First, a permeability factor with a range from 2 to 10 is input. Guidance for selection of an appropriate permeability factor is given, infra. However, the inventor has found that acceptable results are achieved upon operator selection of any number between 2 and 10. Next, a body size option is input. At this point, the user has a choice to use a standard model which will include a 5,000 milliliter blood volume and standard cardiac output of 6500 ml/min or a user may input specific information. If specific information is input, the standard blood volume and standard cardiac output are adjusted to conform to the patient's specific information. Blood volume (BV) and cardiac output (CO) can be predicted from the weight (W) in pounds and height (H) in inches of a patient using regression formulae available in standard cardiovascular physiology references. The formula for an adult male with a weight (W) ranging from 100 to 310 pounds, and a height (H) ranging from 60 to 74 inches is:

$$BV = 33.164 * H^{0.725} * W^{0.425} - 1229.$$

For an adult female with weight (W) ranging from 80 to 290 pounds and height (H) ranging from 60 to 74 inches the formula is:

$$BV = 34.85 * H^{0.725} * W^{0.425} - 1954.$$

For an adult male or female, the cardiac output (CO) is given by the formula:

$$CO = 36.36 * H^{0.725} * W^{0.425}$$

In the model, an adjustment to these variables was made as follows. The ratio of the predicted blood volume to the standard blood volume was calculated. This ratio was then applied to the regional blood volume and extravascular fluid volume in the cardiovascular model so the entire body fluid volume was corrected. The cardiac output and regional blood flow were also modified in the same fashion. Consequently, the regional blood flow, blood volume, and distribution of body fluid in the model can be adjusted for subjects of different body weight, height, and gender.

Cardiac output can be further adjusted based on age using the formula:

$$CO = 6500 \text{ ml/min} * (1 - 0.008 * (\text{age} - 30)).$$

When inputting patient specific information, a choice can be made to further adjust the cardiac output for normal, low, and high. The cardiac output level can be estimated using sequential CT scanning of the aorta.

Next, a contrast agent concentration is input and accepted as well as an injection method, total injection time, and injection rate. These values are all well known to those of ordinary skill in the art for particular types of CT scans. Thereafter, control is returned to the main program. The second step of the method is to call the compartment/model subroutine. This subroutine, shown in Figure 8, begins with the right heart and follows the blood flow in the body model diagram shown in Figure 5. A standard input blood flow and vessel volume is assigned sequentially for each circle element representing a vessel compartment in Figure 5. Next, a standard input blood flow, a capillary volume, and an extravascular volume is assigned sequentially for each block element representing an organ

compartment in Figure 5. Thereafter, the blood flow and volume of each vessel and organ compartment is adjusted by the program to be proportional to the ratio of the cardiac output and blood volume of the patient as compared to the standard, as calculated in the patient/contrast subroutine.

In the next step, a differential equation describing the contrast agent transport in each vessel compartment, as derived above, is assigned. If the element is a vessel compartment, a differential equation describing contrast agent transport is assigned. If the element is an organ compartment, two differential equations describing both contrast agent transport in the intravascular compartment and in the extravascular compartment are assigned. Thus, each element in the cardiovascular system is assigned sequentially a differential equation. Control is then returned to the main program.

The next step in the method is to solve the differential equations which were assigned in the compartment/model subroutine to obtain the organ specific concentration. The differential equations are solved with numerical integration programs of the 5th-order Runge-Kutta method to compute contrast agent concentration as a function of time for each compartment.

The concentration of contrast agent in an organ is defined as the ratio of total contrast mass at a specific time to the total volume of the organ. Contrast concentration is converted to CT enhancement in Hounsfield Units (HU) using the ratio 1 milligram I/ml = 25 HU. The relationship between CT enhancement in HU and concentration of contrast agent in mg/ml depends upon multiple factors including the type of contrast agent, the surrounding tissue and other factors related to the CT scanner such as peak kilovolts used (kV_p). The assumed relationship of 1 mg/ml equals 25 HU was arrived at

through an experiment comparing CT attenuation and contrast concentration.

In that experiment, Ioversol-320 (I) was diluted with saline to generate various concentrations ranging from 0 to 30 mg/ml. Fifty ml deposits of the solutions were placed in plastic jars and scanned with a Siemens Somatom Plus CT scanner using standard abdomen and chest settings of 120 kV_p and 137 kV_p. CT attenuation was recorded by placing a 1.5 centimeter circular region of interest in the center of each jar on each image. Enhancement was computed as the difference between CT attenuation in each jar and the CT attenuation in a jar filled with normal saline. Figure 9 is a graph showing the recorded enhancement levels ranging from 8 to 800 HU for concentrations ranging from 0 to 30 mgI/ml at each of 120 kV_p and 137 kV_p. When a linear relationship was assumed, an increase in concentration by 1 mgI/ml yielded an approximate increase in contrast enhancement of 25 HU.

The last step in the method shown in Figure 6 is providing a display of the enhancement pattern of the vessels and organs of interest as a function of time. This can be through either a data stream or a graph.

To gauge the accuracy of the invention, simulated graphs were generated for a hypothetical patient using different injection protocols. These simulated graphs were compared to empiric graphs representing actual enhancement level measurements in patients who had undergone contrast enhanced CT scans. The empiric graphs represent an average of the recorded enhancement levels in the aorta and liver from three groups of 25 to 28 patients for the injection protocols listed in Table 6 below. Each injection consisted of 125 milliliters of Ioversol-320. The data used to create the empiric enhancement graphs was collected in an unrelated experiment regarding enhancement levels and both uniphasic and biphasic injection protocols. A biphasic

injection uses two injection rates during the injection time. A uniphasic injection uses one injection rate during the injection time.

The simulated graphs represent contrast enhancement for each of the three protocols in Table 6 based on a hypothetical patient whose weight equalled the average weight of the corresponding empirical group of patients. Thus, each point on the empiric graphs represents an average of a wide range of empirical enhancement values while each point in the simulated graphs represents a single enhancement value for a hypothetical patient. Figure 10 shows a simulated graph 100 and an empiric graph 102 for the biphasic-low flow rate injection protocol shown in Table 6. The hypothetical patient, whose enhancement levels are represented in the simulated graph 100, had an assumed body weight of 158 pounds. This assumed body weight was equal to the average body weight of the 28 patients whose actual mean enhancement levels are represented by the empiric graph 102.

Figure 11 shows a simulated graph 104 and an empiric graph 106 for the uniphasic-low flow rate injection protocol in Table 6. The hypothetical patient, whose enhancement levels are represented in the simulated graph 104, had an assumed body weight of 171 pounds. This assumed body weight was equal to the average body weight of the 25 patients whose actual mean enhancement levels are represented by the empiric graph 106.

Figure 12 shows a simulated graph 108 and an empiric graph 110 for the uniphasic-high flow rate injection protocol in Table 6. The hypothetical patient, whose enhancement levels are represented in the simulated graph 108, had an assumed body weight of 177 pounds. This assumed body weight was equal to the average body weight of the 27 patients whose actual mean enhancement levels are represented by the empiric graph 110.

The simulated and empirical contrast enhancement graphs were compared according the maximum enhancement level of each graph and the percent difference between the graphs. The simulated graphs were in good agreement with the empiric graphs. For example, in Figure 10, for the biphasic-low flow rate injection protocol the simulated maximum aortic enhancement was 142.7 HU while the empiric maximum aortic enhancement was 163.4 HU. Also in Figure 10, the simulated maximum hepatic enhancement was 53.8 HU while the empiric maximum hepatic enhancement was 55.5 HU.

In Figure 11, for the uniphasic-low flow rate injection protocol, the simulated maximum aortic enhancement was 220.4 HU while the empiric maximum aortic enhancement was 205.8 HU. Also in Figure 11. the simulated maximum hepatic enhancement was 63.8 HU while the empiric maximum hepatic enhancement was 59.8 HU.

In Figure 12, for the uniphasic-high flow rate injection protocol the simulated maximum aortic enhancement was 321.3 HU while the empiric maximum aortic enhancement was 313.7 HU. Also in Figure 12, the simulated maximum hepatic enhancement was 63.6 HU while the empiric maximum hepatic enhancement was 60.8 HU.

The total mean difference in maximum enhancement between the simulated and empiric graphs was 7.4 percent for aortic enhancement and 4.8 percent for the hepatic enhancement. As can be seen in Figures 10, 11 and 12, the simulated and empiric graphs were also nearly identical in variation over time. Specifically, the average enhancement difference between the simulated and empiric graphs for all three protocols in Table 6 was 11.6 percent for aortic enhancement and 12.7 percent for hepatic enhancement.

It is well known that body weight is one of the patient variables which most drastically affects contrast enhancement. To confirm the functionality of the

invention, the effect of body weight on contrast enhancement was simulated in a hypothetical patient. Figure 13(a) shows simulated aortic enhancement graphs and Figure 13(b) shows simulated hepatic enhancement graphs for uniphasic-high injection protocol in an adult male with a fixed height (5'8") and body weights of 110, 150, 200 and 250 pounds. The simulated graphs demonstrate that contrast enhancement was greatly affected by body weight. For example, in Figure 13(a), the peak aortic enhancement in a subject weight 110 pounds was more than twice that in a subject weighing 250 pounds. However, as expected, the timing of the aortic and hepatic peaks did not vary significantly because alteration in the cardiac output was compensated by alteration in the blood and body fluid volume. The simulated graphs in Figure 13 correlate well with empiric observations in patients showing an inverse relationship between body weight and contrast enhancement.

In the patient/contrast subroutine, selection of a permeability factor between 2 and 10 is required, as explained, infra. However, of the variables used to construct the cardiovascular model, the least is known about the transcapillary permeability. Permeability varies from organ to organ and depends, in part, on the substance being transferred. Organs with discontinuous capillaries such as the liver, spleen and bone marrow have relatively high permeability. Fenestrated capillaries in the kidney and intestines have intermediate permeability. Continuous capillaries in the heart muscle and skin have smaller pores and thus lower permeability.

Although some general information about permeability is known, knowledge about specific transcapillary permeability is limited. For example, the size of the contrast substance is one of the most important properties in determining the rate of

transcapillary exchange. Permeability for different substances will vary according to each substance's molecular weight. Most nutrients and metabolites including glucose (mw=180) and sucrose (mw=342) are quite
5 readily diffusible.

When transcapillary exchange occurs slowly relative to the blood flow rate, it is primarily diffusion-limited. Conversely, if transcapillary exchange occurs rapidly relative to the blood flow rate,
10 it is primarily flow-limited. Iodinated contrast agents consist of relatively small molecules with molecular weights between 800 and 1600. Such contrast agents are distributed rapidly and extensively outside the blood vessels to the entire extracellular fluid within a few
15 minutes of injection and are highly diffusible. Therefore, in the model, it was assumed that the transport of contrast agents to be mostly flow-limited and this assumption was applied equally to every organ in the cardiovascular model.

20 Permeability (P) and transfer area (S) are usually treated as a unit because of the difficulty evaluating them separately without very detailed anatomical information. The permeability-surface area product (PS) is referred to as the "capillary transport coefficient."
25 The magnitude of PS in an organ is frequently expressed relative to the blood flow rate, Q. If PS/Q is larger than 1, the transport is flow-limited. If PS/Q is less than 1, it is diffusion-limited. In an effort to determine acceptable PS values in the model, simulated CT
30 enhancement graphs were generated for several different PS/Q values. The simulated graphs are shown in Figure 14(a) for aortic and Figure 14(b) for hepatic for PS/Q values equal to 0.1, 1, 2, 20 and infinity.

35 Simulated graphs were also generated assuming no transcapillary barrier between the capillary and extracellular spaces, i.e., a single compartment

representing each organ. The simulated CT enhancement graphs generated by the invention with $PS/Q=20$ closely approach those obtained by ignoring the transcapillary barrier. Thus, this PS/Q value is near the upper limit of flow-limited capillary transport. The simulated graphs shown in Figures 14(a) and 14(b), when compared with empiric graphs, confirm that the transport of contrast agent follows a flow-limited process, especially in richly perfused tissues.

10 Figures 15 and 16 show sample aortic and hepatic enhancement levels generated by the invention in data format and graph format, respectively. Operation of the invention can be best understood by referring to Figure 15. Prior to performing a CT scan, an operator inputs
15 the patient specific information, such as height weight and cardiac output, and an injection protocol into the program in accordance with the above description of the invention. The program then generates output data showing the predicted organ specific enhancement values
20 as a function of time. The output data can take the form of a data stream as shown in Figure 15 or a graph as shown in Figure 16.

 The operator views the data initially to determine whether the proposed injection protocol will result in an
25 acceptable enhancement level for an acceptable duration. If the data shows that the desired enhancement level will never be reached, or will not be sustained for a sufficient length of time, the operator chooses a different injection protocol and then reruns the program
30 until a satisfactory predicted enhancement level is obtained.

 After the operator obtains an output showing an acceptable predicted enhancement level and duration, the operator then selects a scan start time and duration,
35 including an appropriate collimation thickness and table speed. In the alternative, all or a portion of the

selection can be performed by the computer. This information is then input into the CT scanner, if obtained off-line from the CT control computer, and the scan is then executed. For example, assuming a threshold hepatic enhancement level of 50, the data of Figure 15 shows that the threshold enhancement level is not reached until .64 minutes after the injection of contrast agent into the patient. In addition, the data shows that the threshold enhancement level will be maintained for approximately 1.7 minutes. Using this information, an operator inputs the scan start time, scan duration, collimation thickness and table speed into the CT scanner and thereafter performs the scan on the patient. In the alternative, computer software can be implemented to automatically transmit the output information directly into the CT scanner.

The program of the invention gives an output which includes a predicted enhancement level in the tissue of interest as a function of an elapsed time after injection. As discussed above, the enhancement threshold is a level of tissue enhancement below which results in a poor quality scan. The scan duration is the time between starting the scan and ending the scan. In order to optimize the scan, the tissue scanned must maintain an enhancement level equal to or greater than the threshold enhancement level for the entire scan duration.

The inventors herein have further expanded the invention by providing a means for analyzing the generated predicted enhancement function (enhancement level with respect to time) to determine if the predicted enhancement level in the tissue to be scanned sufficiently meets the criteria required for an optimum scan and providing a means for adjusting the injection protocol until the output is acceptable.

In the preferred embodiment, preferably implemented in a computer program, if the output

predicted enhancement function indicates that the tissue enhancement level will never attain the desired enhancement threshold or that the tissue enhancement level will not be maintained above the desired threshold for a period of time equal to or exceeding the scan duration, the program provides a means for adjusting the injection protocol.

Referring to Figure 18, the output of the preferred embodiment is a graph or curve 150 showing a predicted enhancement level as a function of time superimposed on a line 152 representing the enhancement threshold. When the peak enhancement, the highest level reached by curve 150, is below the desired threshold, or when the time interval (B-A) is shorter than the desired scan duration, enhancement level must be raised to obtain an acceptable scan. In the graph of Figure 18, enhancement curve 150 exceeds the enhancement threshold for time period (B - A).

If the peak enhancement does not reach the threshold or if the time interval (B-A) is not equal to or greater than the desired scan duration, the preferred embodiment provides the operator two options to increase the predicted enhancement level. It is known in the art that increasing contrast volume, flow rate, or concentration increases the level of enhancement. Because enhancement level is a function of the amount of contrast transported through a particular tissue over a given time period, increasing flow, volume and concentration all result in increased enhancement levels. In the majority of the injector systems, volume and flow rate are easily adjusted through the injector system controls. In addition, most medical facilities have a limited number of differing concentrations. Therefore, the most practical adjustments to adjust enhancement levels are to volume and flow rate. However, adjusting concentration is also acceptable to raise enhancement.

The steps of this aspect of the preferred embodiment are shown in the flow chart of Figure 21. After receiving an input of a predicted contrast enhancement function, an enhancement threshold and a scan
5 duration, the program determines if the predicted enhancement function exceeds the threshold for a time period greater than the scan duration. If not, the operator has the option of either (i) increasing the contrast volume or (ii) increasing the flow rate. After
10 receiving new volume, flow rate or both, the program determines if the maximum allowable flow rate or maximum allowable volume have been reached. It is known in the art that injection flow rates and volumes have maximum limits above which safety concerns are implicated. These
15 limits vary depending on many factors including the particular patient, the contrast agent and the particular procedure involved. Therefore, the present invention provides for the input of maximum values for flow rate and volume. When either the maximum allowable contrast
20 volume or injection rate is reached without achieving the threshold enhancement level, the program continues to allow increasing the other until both maximums are reached. After input of new values, the program iterates the steps of updating the predicted enhancement function
25 based on new values. The contrast volume or the flow rate is progressively increased in this fashion until the time interval (B-A) becomes equal to or greater than the requested scan duration.

In the preferred embodiment, once the volume and
30 flow rate have reached the maximum values, and the predicted enhancement function does not exceed the threshold for a time period greater than or equal to scan duration, the program notifies the operator that a new enhancement threshold must be chosen.

35 Although the preferred embodiment allows the operator to input different flow rates and volumes, the

entire process could be automated and performed by a computer processor. For example, as an alternative to the operator selecting the flow rate and volume to obtain an acceptable enhancement level, a linear bisection
5 method, or other known mathematical process, could be programmed into the computer to solve for a convergence point by reducing the differences between and updating two boundary values.

Although a variance in cardiac output may affect
10 the level of enhancement in a given tissue, the inventors herein have discovered that a change in cardiac output will more dramatically affect the time at which a particular level of enhancement will be achieved. However, the program selects a cardiac output believed to
15 be most closely associated with the patient and uses that value in its computation of the predicted enhancement function. The program also provides for operator input of alternative values for cardiac output with each resulting enhancement function being tested using the
20 above described method. In this way, an operator can be certain that a specific injection protocol will result in a predicted enhancement function which exceeds the desired threshold for the entire scan duration regardless of the cardiac output of the patient.

25 As shown in the flow chart of Figure 21, when the predicted duration of the enhancement (B-A) is greater than the requested scan duration, the method of the present invention allows the operator to select from the options of (i) reducing the volume of the contrast medium
30 or (ii) reducing the injection rate; or (iii) maintaining the current enhancement level and searching for the optimal scan interval within A and B. Options (i) and (ii) may be used for a more efficient scan or for reasons related to a patient's medical history. For example, by
35 reducing the volume of the contrast medium, costs are saved and the patient need not be given unnecessary

additional contrast to create an acceptable scan.

Because the contrast medium might have side effects on the patient, reducing the amount of contrast may be desired to limit the amount of contrast a patient must receive in order to undergo a successful CT scan.

As shown in the flow chart of Figure 21, the process steps of decreasing the volume and/or rate are virtually identical to the method of increasing these values, except for the direction of adjustment, and the discussion above related thereto is equally applicable here. It is also foreseeable that the process steps for increasing and decreasing the flow rate and/or volume could both be utilized in one scan procedure, if for example, an adjustment in one direction resulted in too great a change in enhancement level or, after lowering the threshold, the enhancement level is predicted to exceed the revised threshold for an excessive period.

In the alternative, or if the above concerns are not a factor, as mentioned above in option (iii) the preferred embodiment allows the option of maintaining the selected injection protocol and determining the optimum interval between time A and time B which is equal to the scan duration and during which the tissue enhancement level is the greatest. The method described initially herein was a significant improvement over the prior art in that it allowed prediction, prior to injection, of whether the enhancement level would exceed the threshold value or whether modifications were required in the various input parameters to obtain a tissue enhancement level which exceeded the threshold value for the scan duration. In this fashion, an operator can determine the proper delay after initiating the injection to begin scanning as well as an optimum scan duration. This information also enabled the operator to change various scan parameters, including table speed and collimation thickness in order to achieve a scan during the time when

the tissue enhancement level exceeded the threshold level.

Under certain circumstances, the predicted tissue enhancement function exceeds the threshold enhancement level for a time period greater than the scan duration. The operator could choose arbitrarily at what point after the tissue enhancement level exceeded the threshold to begin the scan, as long as the scan would be completed before the tissue enhancement level decreased below the threshold level and obtain an acceptable scan. Building further on the invention, the inventors herein have provided a means for selecting a scan start time to cause the scan to take place during the optimum temporal window between time B and time A if the duration of predicted enhancement above threshold exceeds the scan duration by more than a predetermined amount of time. As shown in the flow chart of Figure 21, when the time interval (B-A) is equal to (or approximately 10 % greater than) the expected scan duration, point A becomes the onset of scanning. Thus, the optimal temporal window of scanning begins at time A and ends at time B. If, however, the time interval (B-A) is significantly greater than the expected scan duration plus 10%, the invention selects an optimal temporal window within B-A by maximizing the predicted enhancement available. This is best understood by referring to Figure 19.

In Figure 19, the enhancement curve or function of the tissue to be scanned is displayed along with a desired threshold of enhancement on a graph of enhancement versus elapsed time after injection. As shown, the enhancement level of the tissue to be scanned increases from level 0 at time 0 to a level equal to the desired enhancement threshold at time A. The tissue enhancement level continues to rise to a peak enhancement level above the threshold and then decreases to again equal the desired threshold at time B. After time B, the

tissue enhancement level continues to decrease below the threshold. As is known in the art, a uniphasic injection results in a single peak enhancement level being attained as shown in Figure 19. Thus, the duration of predicted
5 enhancement above threshold is represented as (B-A).

Referring still to Figure 19, the method of the present invention selects two points (C and D) whose difference (D-C) is equal to the scan duration and between which the area under the enhancement curve above
10 the threshold (AUC) is maximized. As executed in one of the steps of the flow chart of Figure 21, a set of AUC's are calculated as point C incrementally advances with a fixed interval (D-C) to determine the optimum scan interval. The first AUC is calculated when C coincides
15 with A. This would correspond to beginning the scan at the time the tissue enhancement level first equals the threshold value. The last AUC is calculated when D coincides with B. This would correspond to ending the scan when the tissue enhancement level equals the
20 threshold level for the second time. After calculating the set of AUC's, choosing the maximum AUC sets the optimal scan start time (C) and scan end time (D).

The number of AUC's in the set is dependant on the increment with which C is advanced. Of course, the
25 smaller the increment of advancement, the more accurate on average the time interval predicted for optimal scanning will result. The inventors herein have found that calculating the AUC's while incrementally advancing C in units of 1 second is satisfactory. When the
30 enhancement curve is uniphasic, a plot of the set of AUCs demonstrates a similar distribution and the optimal scanning interval contains the peak enhancement point. Thus, in a uniphasic scan the maximum AUC should be known once the calculated AUC begins to decrease from a peak
35 value.

Unlike the prior art, the invention initially disclosed herein allows the operator to predict, prior to starting an injection, whether tissue enhancement will successfully attain a threshold, whether the tissue enhancement level will be maintained above the threshold for the entire scan duration, and the proper scan delay to allow the scan to begin at a time when the tissue enhancement level exceeds the threshold value. The above described improvements enhance the invention by providing a means for optimizing the injection protocol to obtain acceptable enhancement levels and optimizing the scan start time when the period of acceptable enhancement is predicted to be greater than the scan duration.

These methods and those initially described are significant improvements over the prior art and allow prediction well within acceptable limits of accuracy. However, the inventors herein have further improved the invention by providing for even more accurate predictions. As explained above, the tissue enhancement level is directly related to the volume and concentration of contrast in the tissue to be scanned when the scan takes place. Because the contrast agent is distributed throughout the patient by the cardiovascular system, the amount of contrast in a given tissue at a given time is related to various patient specific parameters which affect contrast transport throughout the patient. These include height, weight, gender, age, and cardiac output.

Cardiac output, unlike height, weight, gender and age is not readily measured. As explained above, many factors including disease status or prior heart failure may affect cardiac output. In addition, a patient does not maintain the same cardiac output during his or her entire lifetime.

Inputting the correct cardiac output into the model is necessary for accurate prediction of optimum scan delay. For example, if a patient has a poor cardiac

output and the operator uses a standard cardiac output because the cardiac status is unknown, the predicted optimum time to begin scanning a tissue will not coincide with the actual optimum time to begin scanning the
5 tissue. Although the predicted threshold level will eventually be met, the maximum period of enhancement may still not coincide with the period of scanning due to the input of an inaccurate cardiac output.

To account for varying cardiac output, the
10 intention initially described provided for the input of different cardiac output values into the mathematical model of the cardiovascular system. In addition, the invention initially described provided for the operator to choose several alternative values for cardiac output
15 and generate a family of predicted tissue enhancement functions or curves corresponding to the alternative values. By predicting and analyzing the family of curves prior to injection, the operator could be certain that the tissue enhancement level would meet or exceed the
20 threshold enhancement regardless of the cardiac output.

In the later described invention, each family member has a slightly different cardiac output status so that the entire family represents the predicted tissue enhancement functions for the entire spectrum of cardiac
25 output status. Increasing the number of family members increases the accuracy of the prediction for a given patient. For example varying standard cardiac output by 10% between each family member from 10% to 110% will give the predicted tissue enhancement level in ten patients
30 having identical body habitus, except for cardiac output, and the predicted enhancement functions will reflect the difference caused solely by the 10% difference in cardiac output between each patient.

The invention initially described provides for
35 taking actual measurements of enhancement after initiating the injection and comparing the family of

enhancement curves to the actual enhancement curve to determine which family member most closely resembles the actual enhancement levels. In that way, it provides a means for determining early in the scan, before the
5 threshold level had been reached, whether the scan parameters were appropriate and allows for adjustment if necessary.

Although this is a significant improvement over the prior art, the comparison of the family of curves to
10 the actual enhancement measurements in the tissue to be scanned must be performed quickly to allow time to adjust the scan parameters if necessary. Therefore, the later described invention uses a combination of a predicted enhancement function, in a region of interest, such as
15 the aorta, prior to injection, and measurements of actual enhancement levels, after initiation of injection, to calculate a correction factor (such as proper cardiac output status) to be used by the model when predicting a
20 tissue enhancement function for the tissue to be scanned, such as the liver. The preferred embodiment provides for sequential low-dose pre-scanning of the aorta after injection to calibrate the mathematical model to unknown or difficult to measure specific patient parameters such as cardiac output. Because the contrast reaches the
25 aorta quicker than the liver, using enhancement level measurements in the aorta as feed back increases the time allowed to make corrections to the scan parameters before the required onset of hepatic scanning.

The preferred embodiment is implemented in a
30 computer program and can be implemented in a stand alone computer, a computer included in a CT scan machine or a computer included in an injector system. Moreover, the present invention could be implemented in a CT scan system which includes an injector and a CT scan machine
35 both controlled by the same computer. In the preferred embodiment, the computer program contains a mathematical

model of the patient's cardiovascular system. The details of the mathematical model are fully explained above.

The computer program accepts input values for those parameters in the patient and in the injection protocol which affect contrast transport through the cardiovascular system. These include patient age, gender, height, weight, cardiac output and injection flow rate, volume, concentration, phase and scan duration.

10 The program accepts the inputs and generates a predicted enhancement level as a function of an elapsed time after injection for both aortic and hepatic enhancement. Figure 20 shows a table giving the data output from the program for a particular patient having a particular body

15 habitus and presuming a standard cardiac output. The operator has already adjusted the injection protocol using the method set forth above to ensure that the predicted enhancement function will exceed the threshold for a length of time exceeding the scan duration. The

20 columns of information displayed in Figure 20 are as follows: the left most column headed "time" represents elapsed time from the start of injection; the next column to the right displays the calculated predicted hepatic enhancement level in Hounsefield Units; the next column

25 is the difference between the predicted enhancement level and the preselected threshold chosen as 50 Hounsefield Units; and the next column displays the calculated AUC, with each entry being aligned with its corresponding scan start time. For example, the first entry of 9.6

30 corresponds to a scan start time of 40 seconds and a scan end time of 70 seconds. Using the methodology of the present invention, the maximum AUC is readily identified as 263.8 which corresponds to a scan start time of 60 and a scan end time of 90. The start scan and end scan times

35 for the optimal temporal window are identified in the last column of the table of Figure 20.

To enhance the prediction of scan start time, the method of the present invention can be used to update or confirm the output of the table in Figure 20. First, a base line scan is performed at a region of interest prior to the initiation of the injection so as to enable a calculation of the actual enhancement level for the region of interest. The base line scan, as is known in the art, is a low-dose or partial scan in which the x-ray dose is reduced substantially compared to a typical scan and views may be acquired through less than a full revolution of the gantry. The x-ray dose is thus considerably less than a normal image scan, but nevertheless, a slice image may be reconstructed.

In the preferred embodiment, an actual aortic enhancement function is compared with predicted aortic enhancement functions, generated using different cardiac outputs, to calculate a correction factor to be applied to the model before predicting a hepatic enhancement function. After the correction factor is applied, the predicted hepatic enhancement function generated is more accurate than the predicted hepatic enhancement function generated without the correction factor. Although the region of interest monitored can be the tissue to be scanned, it is preferable to monitor a region of interest distinct from, and one which will provide a measured response faster than, the tissue to be scanned to allow for maximum time to calibrate the mathematical model to the particular patient and update the scan parameters. In the preferred embodiment, a region of interest is selected that can be monitored for actual enhancement and analyzed sufficiently before the tissue to be scanned attains a threshold enhancement level. This allows the program to use the feedback from the monitoring to enhance the accuracy of the model which is then used to predict a tissue enhancement function. The more accurate tissue enhancement function can then be used to select

optimum scan parameters well before the onset of scanning.

After the operator has selected an appropriate region of interest and performed a base line scan of the region of interest, the injection is initiated according to the selected injection protocol. After the injection is initiated, and as the injection is being administered, the CT scan machine is used to monitor the region of interest enhancement level using low-dose pre-scan x-rays. The information from the pre-scan monitoring is used by the program to generate an actual aortic enhancement function as shown in Figure 23. As in Figure 23, the predicted 160 and actual 162 regional enhancement function can be displayed on the same graph for comparison. The data generated by the pre-scan monitoring can also be used to display the contrast enhancement level in a chart or to reconstruct an actual image of the region of interest being monitored.

After sufficient time has elapsed, the predicted regional enhancement function can be compared to the actual regional enhancement function generated by the low-dose pre-scanning of the region of interest. The results of the comparison can be used to calibrate the mathematical model for factors such as cardiac output before generating the predicted tissue enhancement level for the tissue to be scanned. Referring to Figure 23, the predicted aortic enhancement function 160 is shown along with the actual aortic enhancement function 162 from pre-scan monitoring.

Also shown in Figure 23 are the originally predicted hepatic enhancement function 164 and an updated or calibrated predicted hepatic enhancement function 168 corresponding to the two aortic curves. As can be seen, due to a measured decreased cardiac output in the patient, the onset of hepatic scanning must be delayed longer than originally predicted. It is this feedback

that is used by the present invention to calibrate or fine tune predicted hepatic scanning based on the actual measurement of aortic enhancement levels with low-dose pre-scanning.

5 The slope of the measured aortic enhancement curve 162 may be calculated at a predetermined time and compared to the calculated slope of the predicted aortic enhancement curve 160 to determine the difference between the predicted and actual patient aortic output. However, 10 this slope comparison has been unreliable as it has been observed that early aortic enhancement measurement is frequently pulsatile and noisy. The inventors herein have discovered that by graphing the actual enhancement as a function of time elapsed after injection (the 15 enhancement curve 162) and measuring the area under the enhancement curve (AHC) after a predetermined time interval, this calculated AHC provides a much more reliable indicator of the patient's aortic output.

 The method of the preferred embodiment plots the 20 actual measurements of aortic enhancement to represent the actual enhancement level as a function of time and calculates the area under the curve (AHC) of the actual aortic enhancement function at a predetermined time. This AHC can be compared to the area under the curve of the 25 predicted regional enhancement function to gauge the accuracy of the model and calculate a correction factor. The present invention is very useful in determining predicted enhancement levels in specific tissue of a patient when not all of the patient specific parameters 30 which affect transport are known. For example, as discussed above, cardiac output is a patient specific parameter which is not readily measurable. However, the differences between a predicted aortic enhancement function and an actual measured enhancement function may 35 be analyzed to determine the cardiac output of a patient. It is known that the delay between aortic and hepatic

enhancement represents the time required to distribute contrast medium from the aorta to the liver and is proportional to the cardiac output. The slower the cardiac output, the longer the delay between the time that contrast medium is delivered to the aorta and the time it is delivered to the liver. Thus, with less than standard cardiac output the onset of hepatic scanning must also be delayed so as to coincide scanning with peak enhancement.

10 The method of the present invention was used to exhibit the effect of cardiac output on contrast enhancement for a hypothetical adult male with a fixed height (5 ft. 8 in.) and body weight (150 lbs) subjected to uniphasic-high injection protocol. The cardiac output
15 specified for the model was varied by multiplying the standard cardiac output by 0.25, 0.50, and 2.0. Four enhancement curves were generated for predicted aortic enhancement as shown in Figure 22(a) and four enhancement
20 Figure 22(b). As can be seen from Figure 22(a), as the cardiac output decreases, the time delay to the peak enhancement increases in both aortic and hepatic enhancement curves. The peak aortic value increases with reduced cardiac output, while in Figure 22(b) the plateau
25 of peak hepatic enhancement is prolonged.

 The method of the present invention is practiced as follows. A look up table can be constructed using the computer program of the present invention to generate different outputs of predicted regional enhancement
30 levels in a region of interest based upon different cardiac outputs. An example of such a table is shown in Figure 24. As shown in the table, predicted aortic enhancement levels are calculated at 5 second intervals for high cardiac output (200%), standard cardiac output
35 (100%), reduced cardiac output (75%) and low cardiac output (50%). The area under the aortic curve is also

calculated at intervals of 5 seconds for each different cardiac output. The last column of Figure 24 shows an example of a list of actual aortic enhancement levels measured from low dose pre-scanning and areas under the 5 actual regional enhancement curve for those enhancements.

A predetermined time after injection is chosen, for example 20 seconds, shown in the last column of the table in Figure 24, the actual AHC at time equal 20 seconds is calculated. The operator (or the computer) 10 can then compare the actual AHC at 20 seconds with the predicted AHCs in the first four columns to determine which column most accurately predicts an AHC of 776 HU*sec. at time 20 seconds. As can be seen from the table, the column having cardiac output equal to 75% most 15 closely matches the AHC at 20 seconds (AHC=768 HU*sec). Once the cardiac output is determined in this fashion, the program can calculate a predicted hepatic enhancement function using cardiac output of 75%. This will allow the prediction of hepatic enhancement with much more 20 accuracy because the model is more closely calibrated to the patient specific parameters which affect contrast enhancement.

The table of Figure 20 was previously explained to determine the optimum onset of hepatic scanning for a 25 patient with a specific body habitus and assuming a standard cardiac output. Using the results of the aortic monitoring, shown in the table of Figure 24, a revised table was generated for the same patient. As described above, the results of the table in Figure 24 reveal that 30 a more accurate cardiac output for the patient is 75% of the standard. Therefore, a new table, shown in Figure 25, was generated for predicting the optimum onset of hepatic scanning. As can be seen comparing Figure 20 to Figure 25, the optimum onset to hepatic scanning is 35 changed from 60 seconds, which was predicted using standard cardiac output, to a delay of 80 seconds,

predicted using cardiac output of 75% standard. The optimum scan interval is determined for the updated hepatic scanning parameters using the present invention by the greatest AHC for the interval of scan duration as
5 discussed above. Thus, the hepatic enhancement levels can be accurately predicted to allow the entire scan duration to take place during an interval of maximum enhancement even if cardiac output cannot be readily measured.

10 Furthermore, the operator, or computer, has sufficient time to modify the scan parameters, such as scan delay, because the calculation of cardiac output was performed at 20 seconds after injection initiation and the onset of hepatic scanning should not occur until
15 approximately 80 seconds after initiation of injection. Although a greater delay before calculating the area under the actual aortic enhancement curve could provide a more accurate outcome, the inventors have found that measuring aortic output at 15-20 seconds after initiation
20 is acceptable and allows sufficient time to update the scan parameters.

An alternative embodiment of the method of the present invention is shown in the flow chart of Figure 26. This embodiment, preferably embodied in a computer
25 program, calls for the creation of an interpolating look-up table showing the times (t_1) that different cardiac outputs reach a predetermined AHC and showing predicted optimum hepatic scanning times (t_1^*) correlated to each (t_1). The input to this embodiment is the actual level
30 of aortic enhancement which is being attained in the patient.

The program uses the input to graph the actual enhancement function and compute at regular intervals the area under the actual enhancement curve (AHC). When the
35 computed actual AHC is equal to the AHC from which the table was generated, the time expired after the injection

initiation is recorded. The recorded time is then used with the table to find the t_1 closest to the recorded time. Once the corresponding t_1 is found in the table, the corresponding optimum time for onset of hepatic scanning (t_1^*) is given. Using the table, the operator can thus obtain the predicted delay prior to beginning the onset of hepatic enhancement well before the time to begin the hepatic scan occurred.

There are various changes and modifications which may be made to the invention as would be apparent to those skilled in the art. However, these changes or modifications are included in the teaching of the disclosure, and it is intended that the invention be limited only by the scope of the claims appended hereto.

52
EXHIBIT A

TABLE 1. ESTIMATED DISTRIBUTION OF BLOOD IN VASCULAR SYSTEM OF AN ADULT HUMAN

| REGION | VOLUME | |
|--------------------------|--------|------|
| | mL | % |
| HEART (DIASTOLE) | 360 | 7.2 |
| PULMONARY | 440 | 8.8 |
| ARTERIES | 130 | 2.6 |
| CAPILLARIES | 150 | 3.0 |
| VEINS | 160 | 3.2 |
| SYSTEMIC | 4,200 | 81 |
| AORTA AND LARGE ARTERIES | 300 | 6.0 |
| SMALL ARTERIES | 400 | 8.0 |
| CAPILLARIES | 300 | 6.0 |
| SMALL VEINS | 2,300 | 46.0 |
| LARGE VEINS | 900 | 18.0 |
| TOTAL | 5,000 | 100 |

MODIFIED FROM THE REFERENCE (MILNOR)

**TABLE 2. ESTIMATED DISTRIBUTION OF CARDIAC OUTPUT IN AN ADULT HUMAN.
THE LIVER RECEIVES DUAL BLOOD SUPPLIES, HEPATIC ARTERY AND PORTAL SYSTEM**

| REGION | BLOOD FLOW | |
|-------------------------|------------|------|
| | mL/MIN. | % |
| UPPER EXTREMITIES | 325 | 5.0 |
| HEAD | 975 | 15.0 |
| CORONARY | 260 | 4.0 |
| BRONCHIAL | 130 | 2.0 |
| KIDNEYS | 1,430 | 22.0 |
| LIVER | 1,885 | 29.0 |
| HEPATIC ARTERY | 455 | 7.0 |
| PORTAL | 1,430 | 22.0 |
| SPLEEN/STOMACH | 430 | 6.6 |
| PANCREAS/INTESTINE | 1000 | 15.4 |
| TRUNK/LOWER EXTREMITIES | 1,495 | 23.0 |
| TOTAL | 6,500 | 100 |

MODIFIED FROM REFERENCE (WADE)

TABLE 3. ESTIMATED DISTRIBUTION OF BODY FLUID IN AN ADULT HUMAN.

| COMPARTMENT | VOLUME (LITER) |
|---------------------|----------------|
| ICF (EXCEPT RBC) | 19.1 |
| ECF (EXCEPT PLASMA) | 15.9 |
| BLOOD (PLASMA+RBC) | 5.0 |
| TOTAL BODY WATER | 40 |

ESTIMATION BASED ON THE VOLUME OF DISTRIBUTION OF IOHEXOL (OLSSON).

TABLE 4. ESTIMATED DISTRIBUTION OF % BLOOD FLOW RATE AND CAPILLARY VOLUME IN AN ADULT HUMAN. REGIONAL CAPILLARY VOLUME IS CALCULATED PROPORTIONAL TO A REGIONAL BLOOD FLOW OF THE TOTAL 122% (THE PORTAL SYSTEM CONTRIBUTES AN ADDITIONAL 22%)

| REGION | BLOOD FLOW | CAPILLARY VOLUME |
|-------------------------|------------|------------------|
| | % | mL |
| UPPER EXTREMITIES | 5.0 | 12 |
| HEAD | 15.0 | 37 |
| CORONARY | 4.0 | 10 |
| BRONCHIAL | 2.0 | 5 |
| KIDNEYS | 22.0 | 54 |
| LIVER | 29.0 | 71 |
| SPLEEN/STOMACH | 6.6 | 16 |
| PANCREAS/INTESTINE | 15.4 | 38 |
| TRUNK/LOVER EXTREMITIES | 23.0 | 57 |
| TOTAL | 100 (122) | 300 |

TABLE 5. ESTIMATED WEIGHT, WATER CONTENT, AND FLUID VOLUME OF VISCERAL ORGANS IN A 70 kg. ADULT. THE LUNG CONSISTS OF 50% PARENCHYMA AND 50% NON-PARENCHYMA TISSUES WHOSE CAPILLARY VOLUMES ARE 150 mL AND 5 mL, RESPECTIVELY.

| ORGAN | WEIGHT (g) | % WATER | FLUID (mL) | FLUID-CAP. |
|--------------------|------------|---------|------------|------------|
| BRAIN | 1,450 | 76 | 1,102 | 1,065 |
| HEART | 300 | 79 | 237 | 227 |
| LUNG | 500+500 | 79 | 790 | 635 |
| KIDNEYS | 300 | 83 | 249 | 195 |
| LIVER | 1,800 | 68 | 1,224 | 1,153 |
| SPLEEN/STOMACH | 170/150 | 70 | 224 | 208 |
| PANCREAS/INTESTINE | 60/1,770 | 70 | 1,281 | 1,243 |
| TOTAL | 7,000 | | 5,107 | 4,726 |

MODIFIED FROM REFERENCES (ICRP, MAPLESON)

TABLE 6. TESTED INJECTION PROTOCOLS

| PROTOCOL | FIRST RATE (mL/SEC) | FIRST RATE VOLUME (mL) | SECOND RATE (mL/SEC) | SECOND RATE VOLUME (mL) | INJECTION TIME (SEC) | NUMBER OF PATIENTS | MEAN (RANGE) OF WEIGHT (lb>) |
|----------------|---------------------|------------------------|----------------------|-------------------------|----------------------|--------------------|------------------------------|
| BIPHASIC-LOW | 2.5 | 50 | 1 | 75 | 95 | 28 | 158 (100-205) |
| UNIPHASIC-LOW | 2.5 | 125 | | | 50 | 25 | 171 (108-241) |
| UNIPHASIC-HIGH | 5.0 | 125 | | | 25 | 27 | 177 (98-300) |

What is claimed is:

1. A method of scanning a tissue in a patient using computed tomography, said patient having a plurality of patient specific parameters, wherein the tissue to be scanned is enhanced with an intravascularly
5 injected contrast agent, comprising the steps of:
 selecting an injection protocol for the contrast agent;
 predicting prior to implementing said injection protocol a tissue enhancement level as a function of an
10 elapsed time after injection based on the injection protocol and said patient specific parameters;
 determining a set of parameters for an optimum scan based on the predicted tissue enhancement level; and
 performing the scan in accordance with the pre-
15 determined set of optimum scan parameters.
2. The method of Claim 1 wherein the step of predicting the tissue enhancement level comprises the steps of:
 providing a mathematical model which describes
5 contrast agent transport throughout the patient's cardiovascular system;
 inputting into the mathematical model as said patient specific parameters patient specific information and contrast agent specific information which affects
10 physiological parameters of contrast enhancement; and
 using the mathematical model to compute a contrast agent concentration as a function of time.
3. The method of Claim 2 wherein the step of providing a mathematical model includes the steps of:
 providing a compartmental model of the human cardiovascular system including vessel compartments
5 representing blood vessels and organ compartments representing organs;

assigning at least one differential equation describing contrast agent transport to each vessel compartment; and

- 10 assigning at least one differential equation describing contrast agent transport to each organ compartment.

4. The method of Claim 3 further comprising the steps of:

assigning a standard input blood flow and a standard vessel volume for each vessel compartment;

- 5 assigning a standard input blood flow, a standard capillary volume, and a standard extravascular volume for each organ compartment;

adjusting the standard input blood flow of each vessel compartment and each organ compartment as being
10 proportional to a ratio of cardiac output of the patient to a standard cardiac output; and

adjusting the standard capillary volume and the standard extravascular volume of each organ compartment as being proportional to the ratio of blood volume of the
15 patient to a standard blood volume.

5. The method of Claim 4 wherein each organ compartment is further subdivided into a capillary compartment and an extravascular compartment and the step of assigning at least one differential equation to each
5 organ compartment includes assigning at least one differential equation to each capillary compartment and each extravascular compartment.

6. The method of Claim 2 wherein the inputting step includes the steps of:

- inputting a permeability factor;
inputting a patient habitus;
5 inputting a patient blood volume;
inputting a patient cardiac output;
inputting a contrast concentration value;
inputting an injection method;

inputting an injection time; and
10 inputting an injection rate.

7. The method of Claim 6 wherein the step of inputting a patient habitus includes inputting the patient's age, gender, weight, and height.

8. The method of Claim 7 wherein the step of inputting the patient blood volume includes the step of computing the patient's blood volume.

9. The method of Claim 8 wherein the step of inputting the patient cardiac output includes the steps of calculating a standard cardiac output and adjusting the standard cardiac output proportional to a ratio of a
5 cardiac output of the patient to a standard cardiac output.

10. The method of Claim 2 further comprising the steps of:

converting the computed contrast agent concentration into the tissue enhancement level as expressed in
5 computed tomography enhancement units; and

displaying the tissue enhancement level in computed tomography enhancement units as a function of time.

11. A method for predicting a tissue enhancement level as a function of time for a specific tissue in a patient receiving an intravascularly injected contrast agent via a specified injection protocol, said method
5 comprising the steps of:

providing a mathematical model of the cardiovascular system of the patient, said model mathematically describing the transport of said contrast agent through said cardiovascular system,

10 inputting into said model a plurality of patient specific parameters which impact the transport of said contrast agent,

using said model to calculate a predicted concentration of said contrast agent in said tissue as a

15 function of time in response to said specified injection protocol, and

displaying said predicted contrast agent concentration as a function of time as representative of said tissue enhancement level as a function of time.

12. The method of Claim 11 further comprising the step of inputting a set of parameters into said model corresponding to said specified injection protocol, said predicted concentrations being responsive thereto.

13. The method of Claim 12 further comprising the step of comparing a minimum threshold value with said tissue enhancement level to thereby determine a start time and time duration of acceptable tissue enhancement
5 level during which a CT scan may be taken.

14. The method of Claim 13 wherein said mathematical model comprises a plurality of compartments representative of significant organs and vessels in said cardiovascular system, each of said compartments being
5 characterized by at least one differential equation.

15. The method of Claim 14 wherein said mathematical model is embodied in a computer program.

16. A computer being programmed for predicting a structure specific CT enhancement level in a patient for a given patient habitus and a specific contrast injection protocol comprising:

5 a computer having a memory;

a computer program in said memory, said program having means for accepting patient specific information and contrast specific information which affect physiological parameters of contrast enhancement and
10 means for computing and outputting operator selected organ specific contrast concentration as a function of time.

17. The computer of Claim 16 wherein the means for computing organ specific contrast concentration comprises a mathematical compartmental model of the human

cardiovascular system including vessel compartments
5 representing blood vessels and organ compartments
representing organs;

at least one differential equation describing
contrast transport to each vessel compartment; and

at least one differential equation describing
10 contrast transport to each organ compartment.

18. The computer of Claim 17 wherein said computer
program further comprises:

means for assigning a standard input blood flow and
standard vessel volume for each vessel compartment;

5 means for assigning a standard input blood flow, a
standard capillary volume, and a standard extravascular
volume for each organ compartment;

means for adjusting the standard input blood flow of
each vessel compartment and each organ compartment as
10 being proportional to a ratio of cardiac output of the
patient to a standard cardiac output;

means for adjusting the standard capillary volume
and the standard extravascular volume of each organ
compartment as being proportional to the ratio of blood
15 volume of the patient to a standard blood volume.

19. The computer of Claim 18 wherein said computer
program further comprises means for further subdividing
each organ into a capillary compartment and an
extravascular compartment and the step of assigning at
5 least one differential equation to each organ compartment
includes assigning at least one differential equation to
each capillary compartment and each extravascular
compartment.

20. The computer of Claim 19 wherein said computer
program further comprises means for converting the
computed contrast concentration into computed tomography
enhancement units and means for displaying the
5 enhancement level of the organ in computed tomography
enhancements units as a function of time.

21. A computed tomography machine comprising:
a computed tomography machine;
a computer having a memory connected to said
computed tomography machine for controlling its
5 operation; and
a computer program in said computer memory, said
computer program having means for predicting a structure
specific CT enhancement level in a patient for a given
patient habitus and a specific contrast injection
10 protocol.
22. The computed tomography machine of Claim 21,
wherein said computer program comprises:
means for predicting prior to implementing an
injection protocol an organ enhancement level as a
5 function of time elapsed after implementing the injection
protocol based on the injection protocol and patient
specific parameters;
means for determining an optimum scan start time and
scan duration based on the predicted enhancement level;
10 and
means for performing the scan in accordance with the
pre-determined scan start time and scan duration.
23. A method of determining a set of parameters for
an injection protocol for scanning a tissue in a patient
using computed tomography, the patient having a plurality
of patient specific parameters, wherein the tissue to be
5 scanned is enhanced with an intravascularly injected
contrast agent, comprising the steps of:
generating a tissue enhancement function comprising
a tissue enhancement level for the tissue to be scanned
as a function of an elapsed time after injection based on
10 the patient specific parameters and a specified injection
protocol; and
determining the set of injection protocol parameters
for an optimum scan based on the predicted tissue
enhancement function.

24. The method of Claim 23 wherein the step of determining the set of parameters for an optimum scan includes using the predicted tissue enhancement function to thereby determine an injection flow rate and a
5 contrast volume which is predicted to cause the tissue enhancement level to exceed a pre-selected threshold value.

25. The method of Claim 24 further comprising the step of adjusting the set of parameters until the tissue enhancement level is predicted to exceed the threshold value.

26. The method of Claim 25 wherein the set of parameters is sequentially adjusted until the predicted tissue enhancement function is maintained above the threshold value for a time period at least approximately
5 equal to a specified scan duration.

27. The method of Claim 26 wherein the step of adjusting the set of parameters includes selecting the injection flow rate and selecting the injection volume.

28. The method of Claim 23 wherein the step of determining a set of parameters for an optimum scan includes determining an optimum scan interval equal to a specified scan duration during which the predicted tissue
5 enhancement function is the greatest.

29. The method of Claim 28 wherein the step of determining the optimum scan interval includes integrating the predicted enhancement function for successive intervals equal to the specified scan duration
5 and selecting an interval having the greatest integration value as the optimum scan interval.

30. The method of Claim 23, further comprising the steps of:

predicting prior to injecting the contrast agent a regional enhancement level as a function of an elapsed
5 time after injection for a region of interest in the

patient based on the patient specific parameters and specified injection protocol;

initiating the injection protocol;

10 sequentially measuring an actual enhancement level in the region of interest at predetermined elapsed times after initiating the injection to generate an actual regional enhancement function;

calculating a correction factor based on the relationship between the predicted regional enhancement
15 function and the actual regional enhancement function;
and

using the correction factor to calibrate the predicted tissue enhancement function.

31. The method of Claim 30 wherein at least one of the plurality of patient specific parameters has an unknown value and wherein the step of predicting a regional enhancement function includes the steps of:

5 providing a mathematical model of a cardiovascular system, the model mathematically describing transport of the contrast agent through the cardiovascular system;

inputting a plurality of alternatives for the unknown patient parameter into the model to generate a
10 set of alternative regional enhancement functions with the set comprising a member for each alternative; and

selecting a predicted regional enhancement function from the set of alternative regional enhancement functions.

32. The method of Claim 31 wherein the step of selecting a predicted regional enhancement function from the set of alternative regional enhancement functions comprises the steps of:

5 comparing the actual regional enhancement function to the members of the set of alternative regional enhancement functions; and

selecting from the set of alternative regional enhancement functions the member which most closely
10 resembles the actual enhancement function.

33. The method of Claim 32 wherein the step of selecting the member from the set of alternative regional enhancement functions includes the steps of:

graphing the members of the set of alternative
5 regional enhancement functions;
graphing the actual regional enhancement function;
integrating the actual regional enhancement graph from start to a predetermined time after injection;
determining which member of the alternative regional
10 enhancement graphs at the predetermined time has an integrated area closest to the integrated area of the actual regional enhancement graph at the predetermined time.

34. The method of Claim 31 wherein the tissue to be scanned is distinct from the region of interest and wherein the step of using the correction factor to calibrate the predicted tissue enhancement function
5 includes the steps of:

inputting into the mathematical model the alternative chosen for the unknown patient parameter which was used to generate the predicted regional enhancement function; and
10 generating a revised predicted tissue enhancement function.

35. The method of Claim 34 wherein the step of determining a set of parameters for an optimum scan includes the step of:

using the revised predicted tissue enhancement function to determine an optimum scan delay to cause the
5 onset of the scanning of the tissue to coincide with a threshold enhancement level in the tissue.

36. The method of Claim 30 wherein the step of sequentially measuring an actual enhancement level is

performed using low-dose pre-scanning of the region of interest.

37. The method of Claim 31 wherein the region of interest is the tissue to be scanned.

38. The method of Claim 31 wherein said mathematical model is embodied in a computer program.

39. A contrast injector system comprising:

a contrast injector;

a computer having a memory connected to said contrast injector for controlling its operation; and

5 a computer program in said computer memory, said computer program having means for predicting a structure specific CT enhancement level in a patient having a specific patient habitus based on a specified injection protocol.

40. The contrast injector of Claim 39, wherein said computer program comprises:

means for predicting prior to implementing the injection protocol a tissue enhancement level as a
5 function of elapsed time based on the injection protocol and the specific patient habitus; and

means for determining an optimum injection flow rate and an optimum contrast volume based on the predicted tissue enhancement level.

41. The contrast injector of Claim 40 wherein the computer program further comprises:

means for accepting an input including a revised injection rate and a revised contrast volume;

5 means for revising the predicted tissue enhancement level based on the revised injection flow rate and the revised contrast volume.

42. The contrast injector of Claim 41 wherein the computer program includes means for implementing the injection protocol using the revised injection flow rate and revised contrast volume.

43. The contrast injector of Claim 42 wherein the contrast injector is in communication with a computed tomography machine and wherein the computer program includes means for signaling the computed tomography
5 machine to perform a scan.

44. A computed tomography system for scanning a tissue in a patient, the patient having a plurality of patient specific parameters, wherein the tissue to be scanned is enhanced with an intravascularly injected
5 contrast agent, the system comprising:

a computed tomography machine;

an injector system in communication with the computed tomography machine;

a computer having a memory, the computer in
10 communication with both the injector system and the computed tomography machine for coordinating their operation; and

a computer program in the computer memory, the computer program having means for predicting prior to
15 injecting the contrast agent a tissue enhancement level for the tissue based on the patient specific parameters and a selected injection protocol.

45. The system of Claim 44 wherein the computer program includes:

means for determining an optimum injection protocol for injection of the contrast agent; and

5 means for implementing the optimum injection protocol.

46. The system of Claim 44 further comprising means for monitoring actual regional enhancement levels in a region of interest in the patient after initiation of the injection protocol.

47. The system of Claim 46 wherein the computer program includes means for receiving and analyzing the regional enhancement levels to thereby confirm the predicted tissue enhancement level.

48. The system of Claim 47 wherein the computer program includes means for revising the predicted tissue enhancement level based on the regional enhancement level.

49. A computer being programmed for predicting a structure specific CT enhancement level in a patient for a given patient habitus and a specific contrast injection protocol comprising:

- 5 a computer having a memory;
- a computer program in said memory, the program having means for accepting patient specific information and contrast specific information which affect physiological parameters of contrast enhancement and
- 10 means for computing and outputting structure specific enhancement levels as a function of an elapsed time after injection.

50. The computer of Claim 49 wherein the computer program further comprises:

- means for optimizing the injection protocol to thereby cause at least a threshold contrast enhancement
- 5 level over a predetermined scan duration; and
- means for communicating the optimum injection protocol to an injector.

51. The computer of Claim 49 wherein the computer program includes:

- means for determining a set of scan parameters for an optimum scan based on the computed enhancement levels;
- 5 means for communicating the set of scan parameters to a CT scan machine.

52. The computer of Claim 49 wherein the computer program includes means for monitoring actual enhancement levels in a region of interest to thereby confirm the computed enhancement levels.

53. A method for determining an injection protocol for injecting a contrast agent into a patient for

enhancing a tissue desired to be scanned with computed tomography, the method comprising the steps of:

5 generating a plurality of predicted tissue enhancement functions based on different patient parameters; and

10 selecting one of said predicted tissue enhancement functions as being close to expected based upon feedback from a low dose scan of a region of interest.

54. The method of Claim 53 wherein the selecting step includes the steps of generating from said low dose scan an actual tissue enhancement function of said region of interest, integrating said actual tissue enhancement
5 function over a predetermined time period, comparing said integrated value with corresponding integrated values for each of the predicted tissue enhancement functions and selecting as desired the predicted tissue enhancement function with the closest integrated value.

55. The method of Claim 54 further comprising the steps of determining a patient parameter based upon the selected predicted tissue enhancement function, and
5 determining a predicted tissue enhancement function for the tissue to be scanned based at least in part on said determined patient parameter.

56. The method of Claim 53 wherein the low dose scan is of a tissue different than the tissue desired to be scanned.

57. A method for determining an injection protocol for injecting a contrast agent into a patient for enhancing a tissue desired to be scanned with computed tomography, the method comprising the steps of:

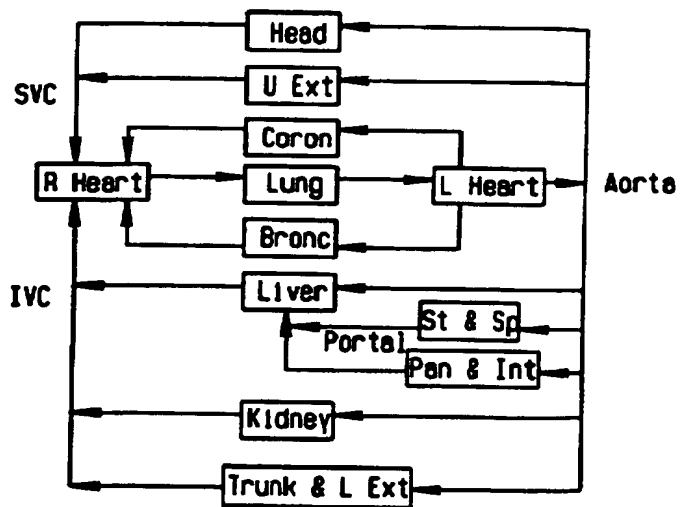
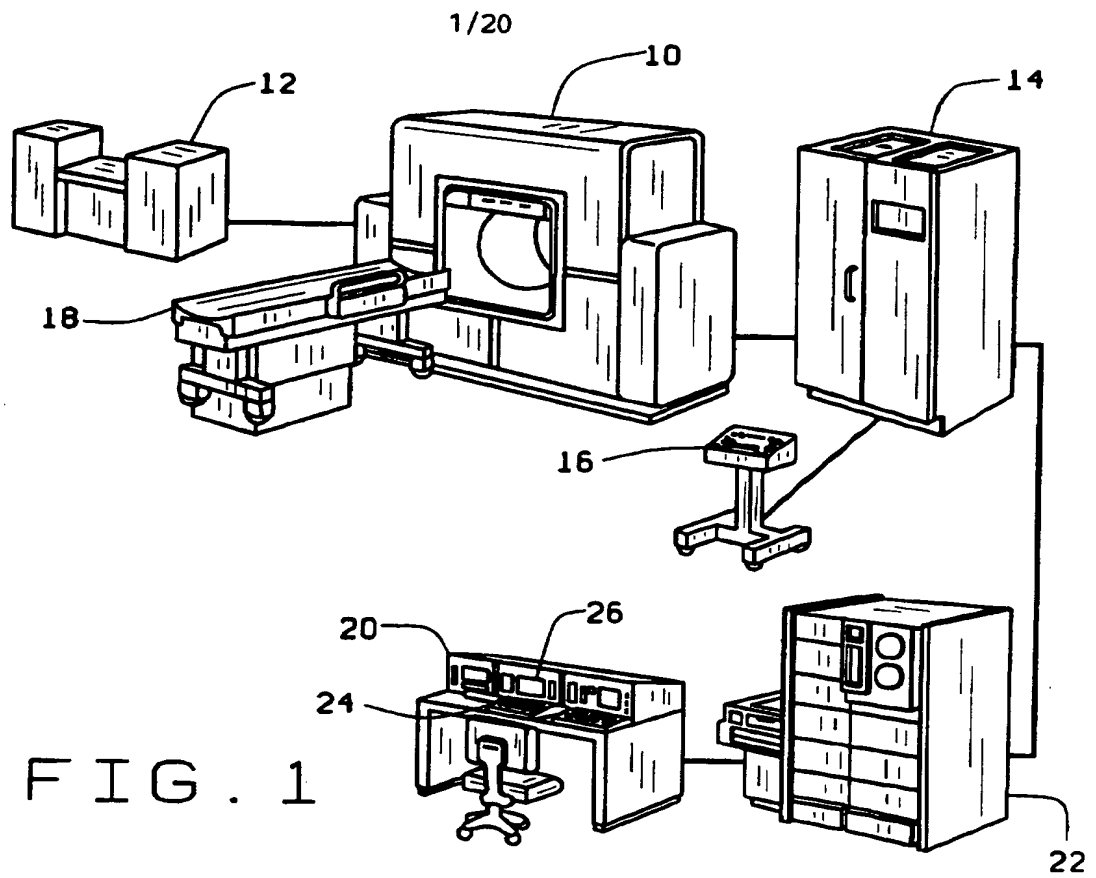
5 generating a predicted tissue enhancement function; selecting a threshold level; and

10 adjusting the injection protocol until the tissue enhancement function remains greater than the threshold level for a time period at least equal to a desired scan duration.

58. The method of Claim 57 further comprising the steps of determining an optimal scan start time and end time by integrating the tissue enhancement function for successive scan duration intervals contained within the
5 portion wherein the threshold is exceeded, and choosing as optimal the integrated interval having the greatest value.

59. The method of Claim 53 further comprising the steps of implementing said method in a computer, and performing a CT scan using said determined injection protocol.

60. The method of Claim 57 further comprising the steps of implementing said method in a computer, and performing a CT scan using said determined injection protocol.



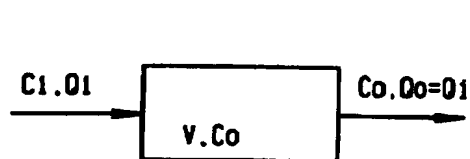


FIG. 3(a)

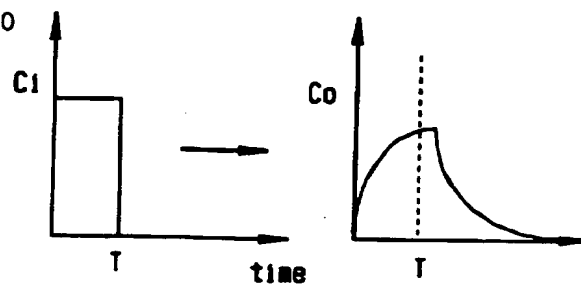


FIG. 3(b)

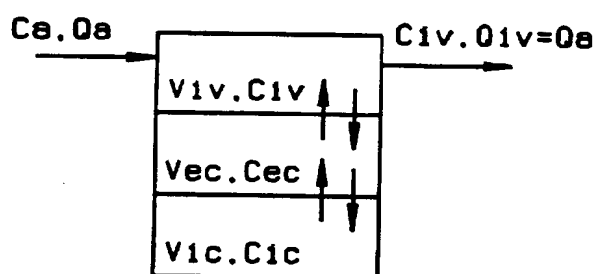


FIG. 4(a)

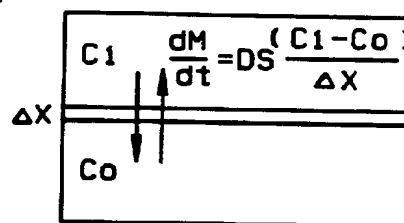


FIG. 4(b)

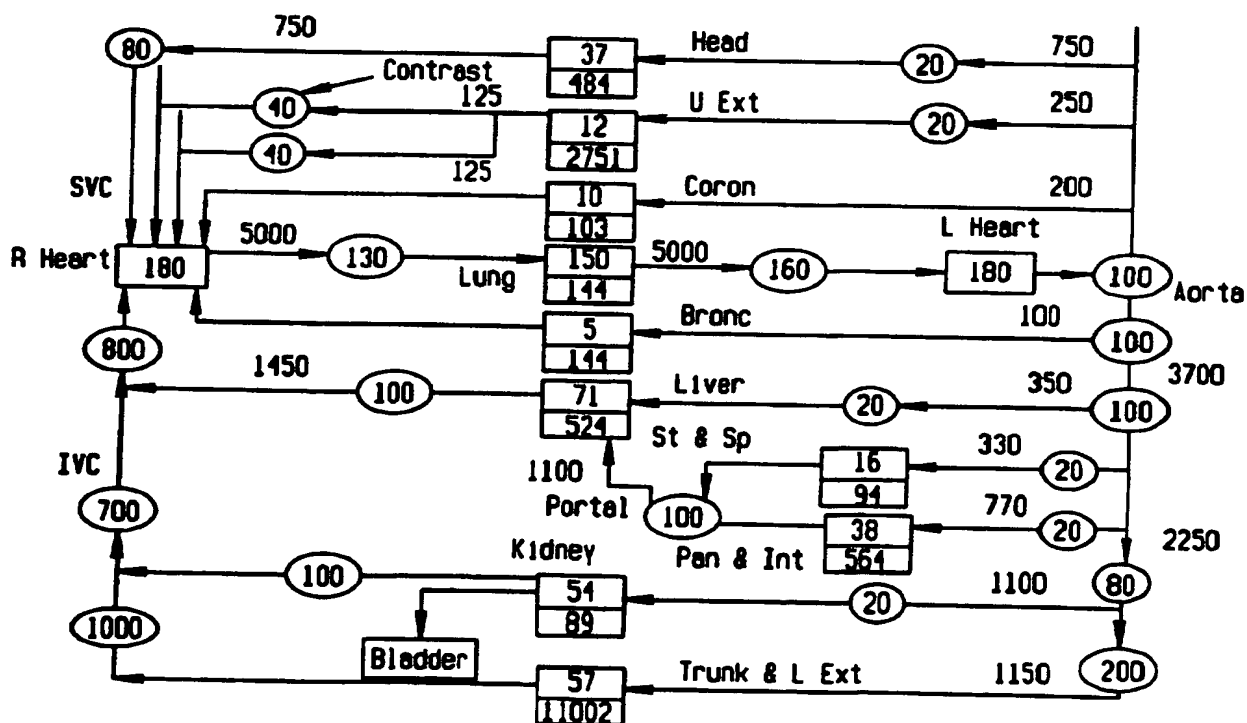


FIG. 5

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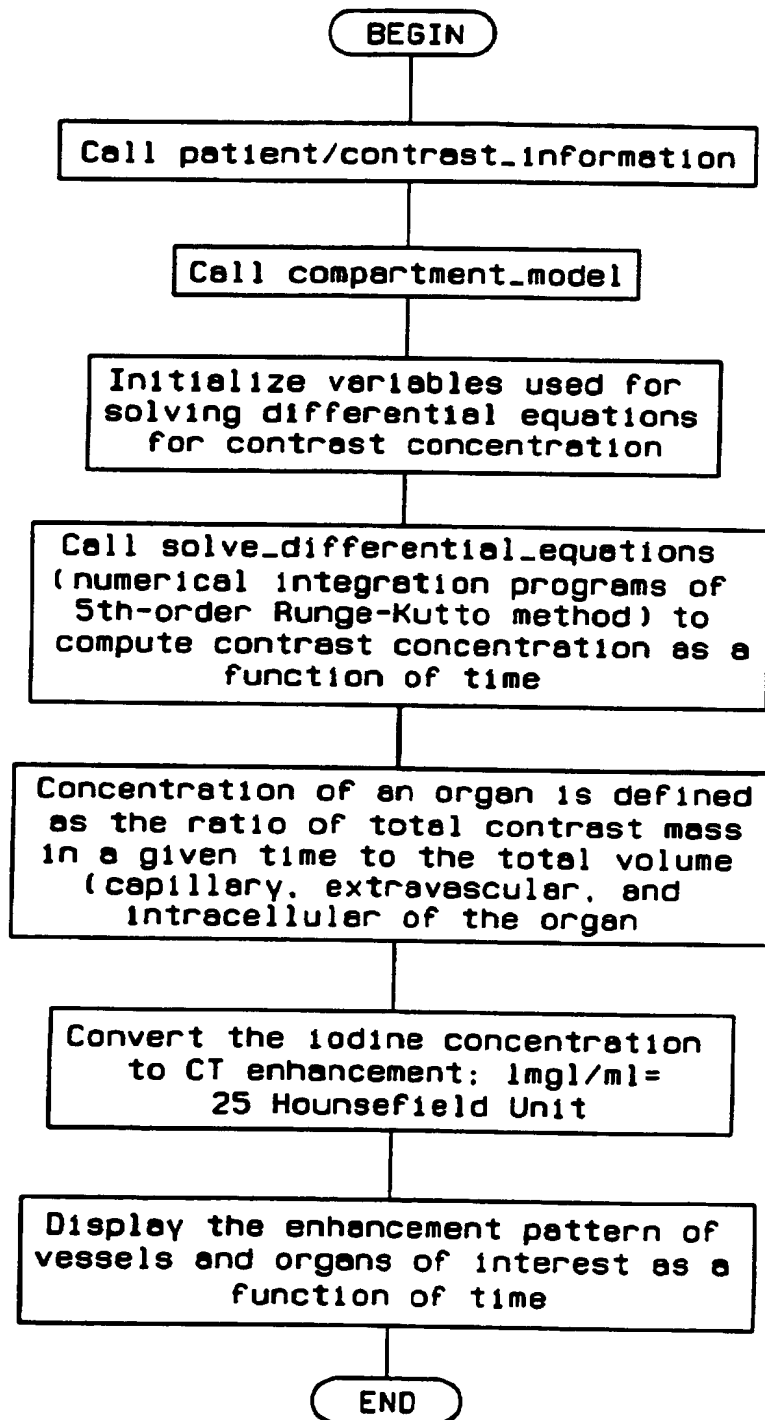


FIG. 6

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Subroutine patient/contrast.Information

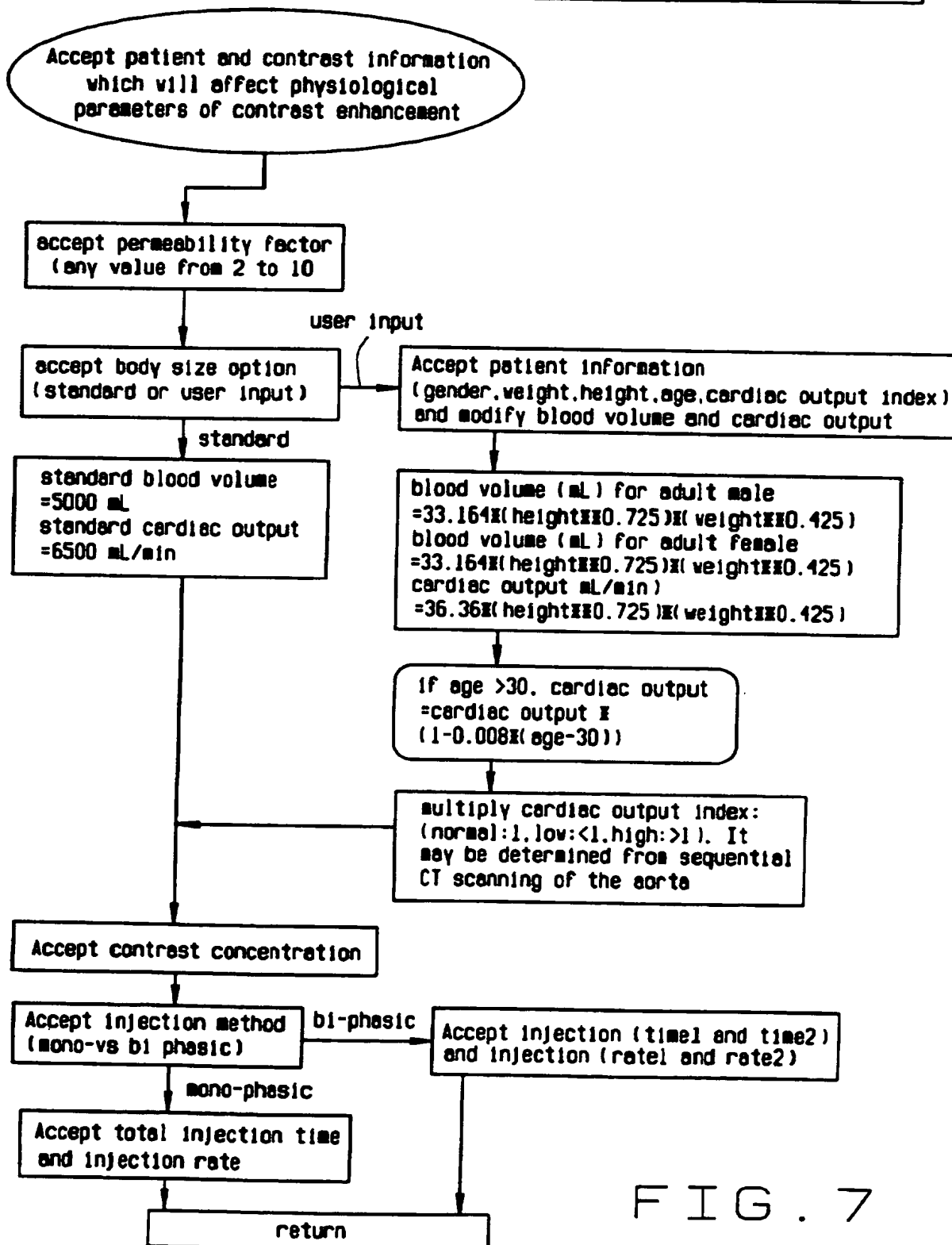


FIG. 7

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Subroutine compartment_model:

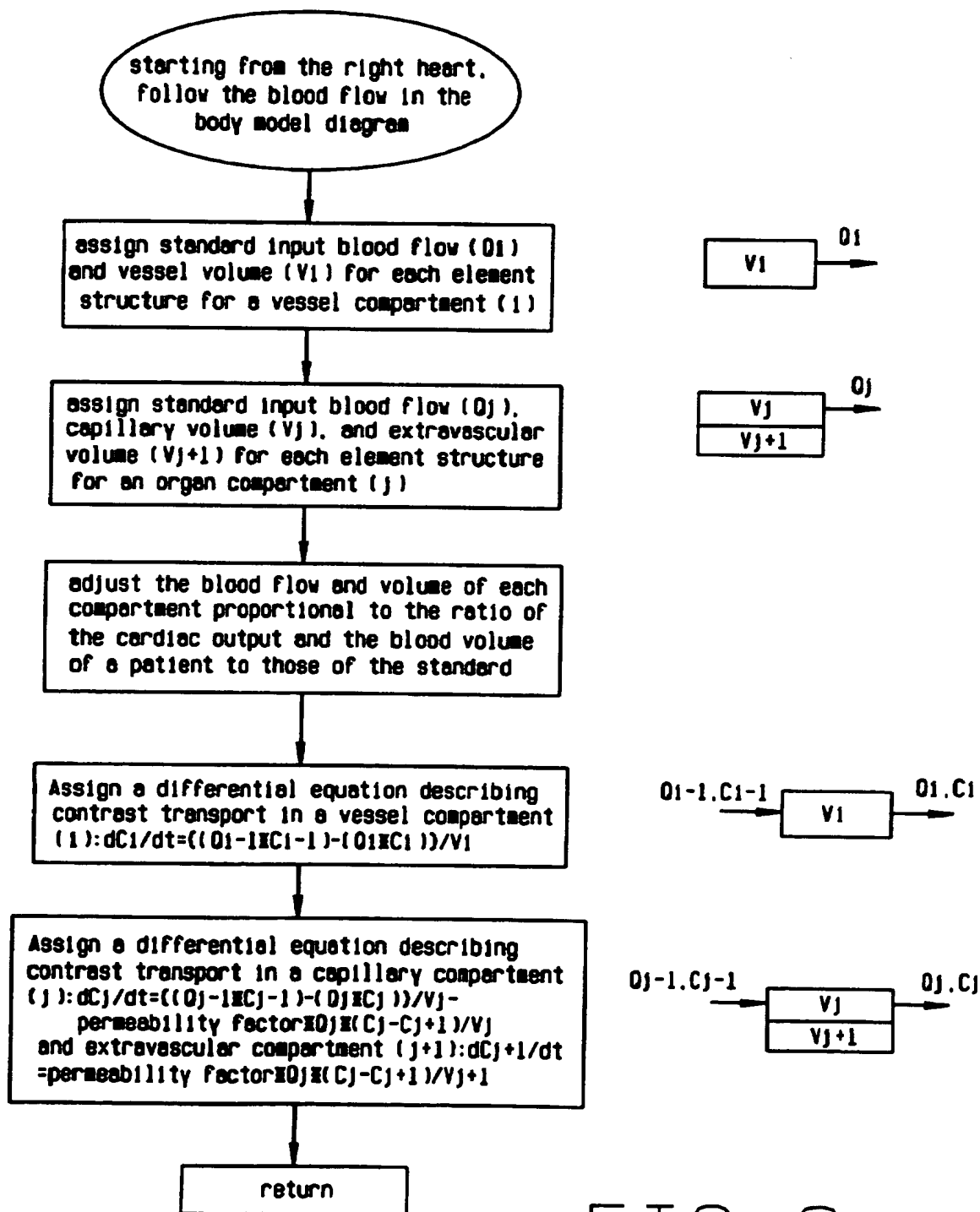


FIG. 8

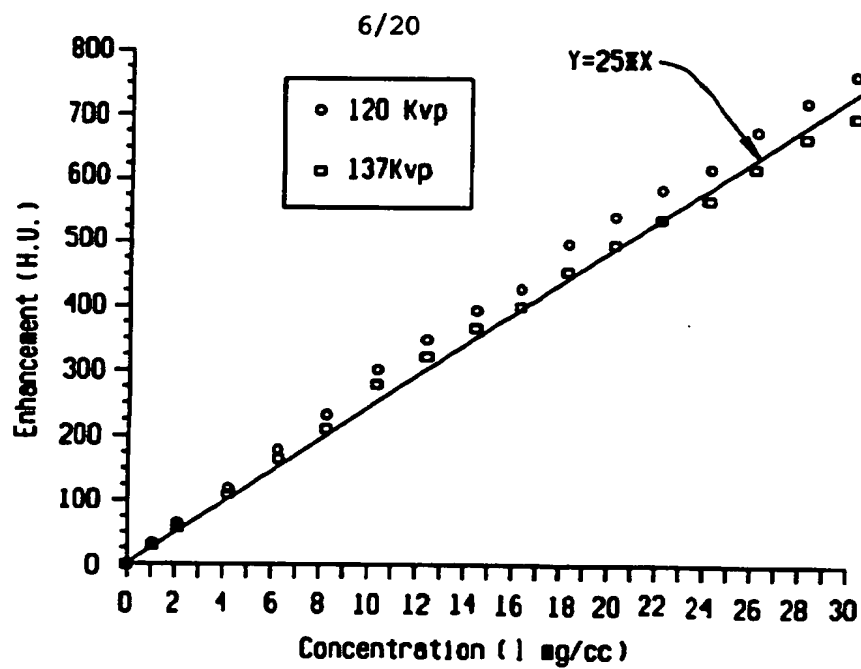


FIG. 9

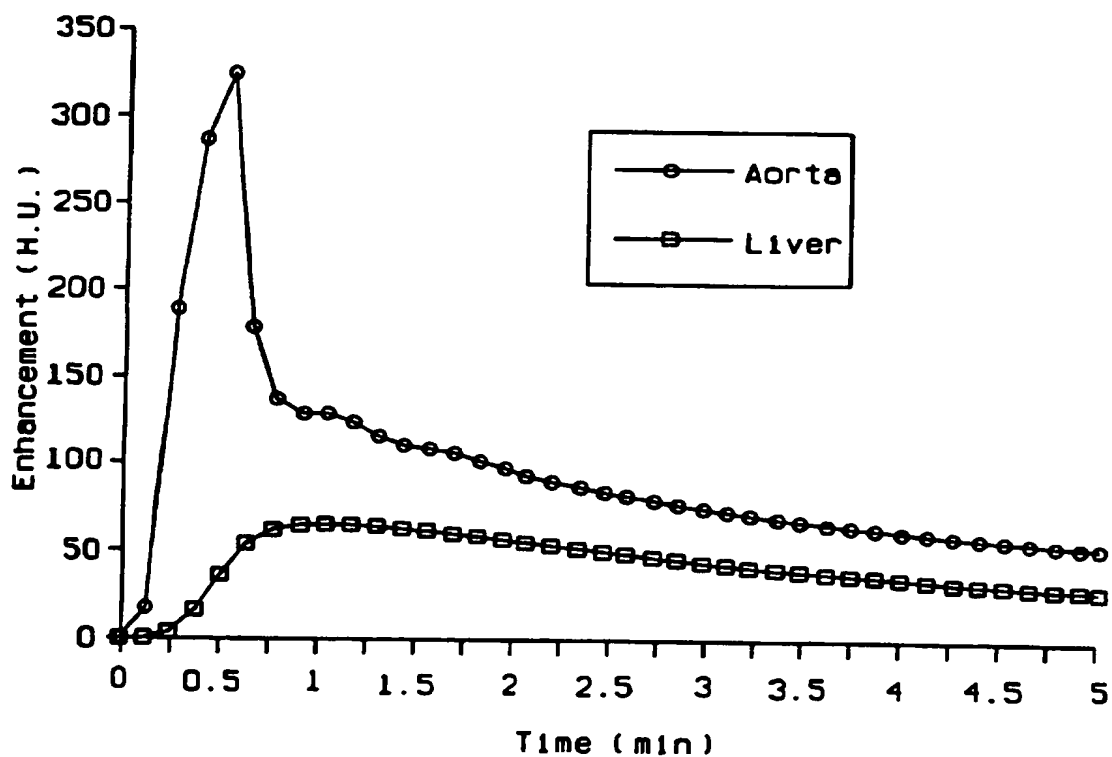


FIG. 16

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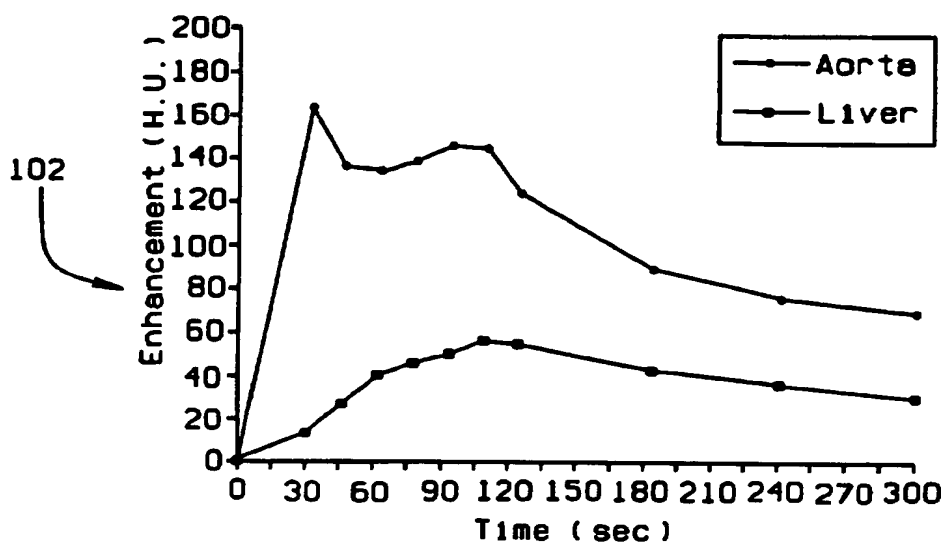


FIG. 10(a)

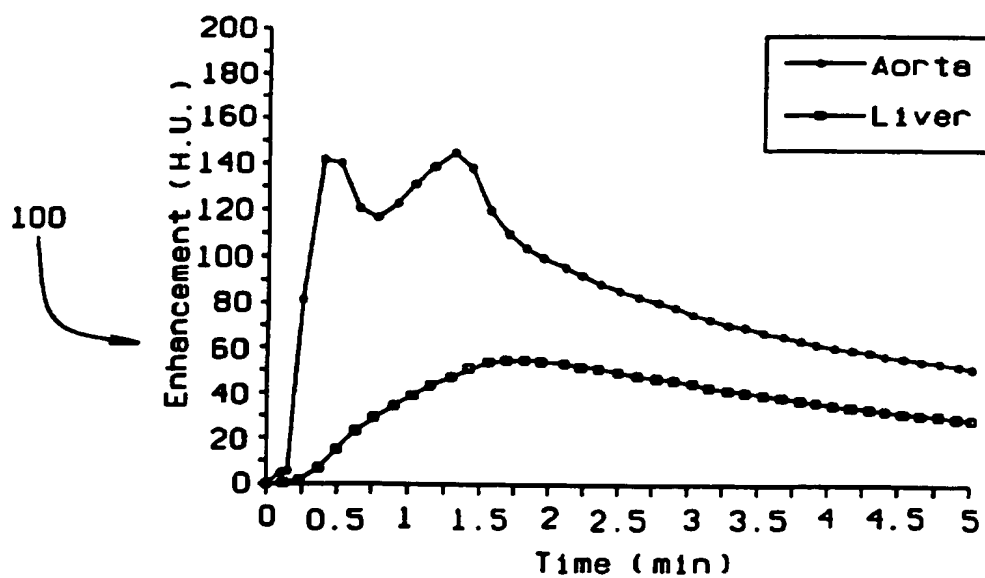


FIG. 10(b)

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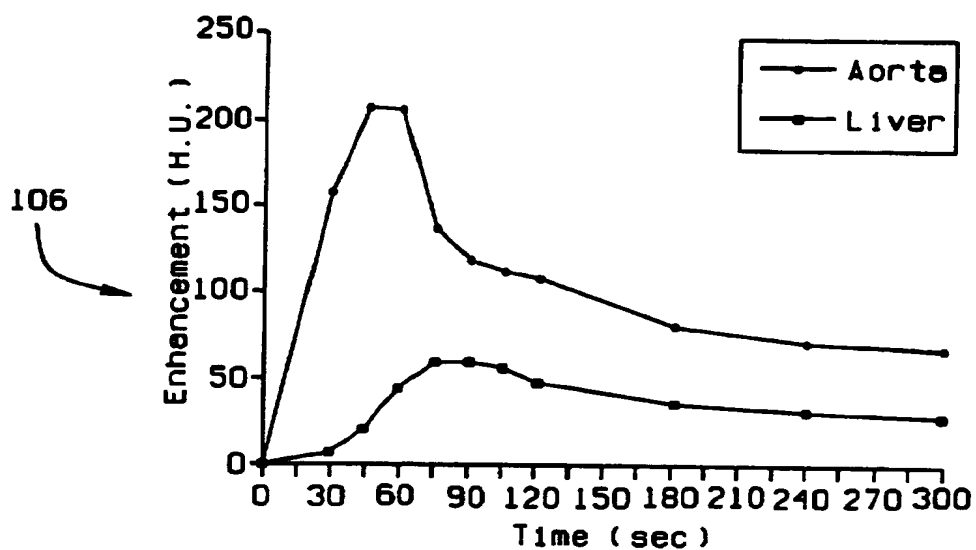


FIG. 11(a)

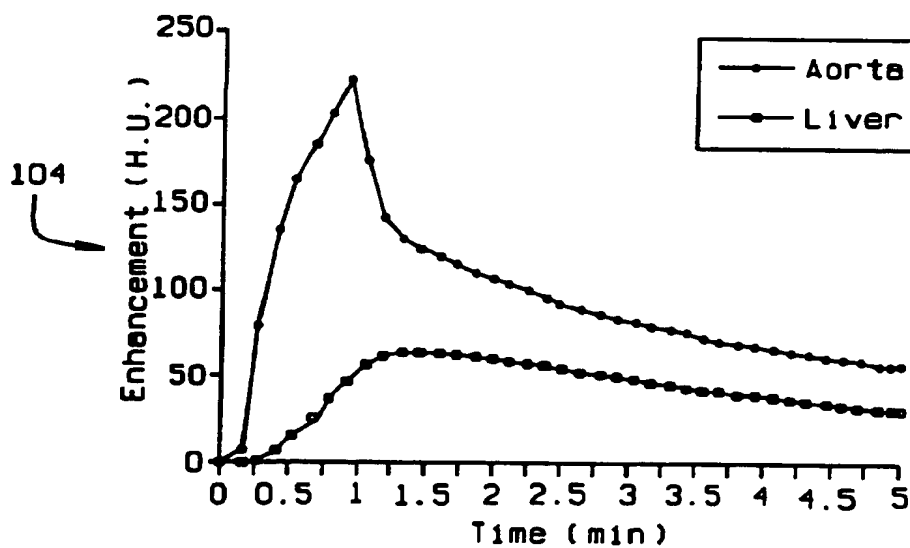


FIG. 11(b)

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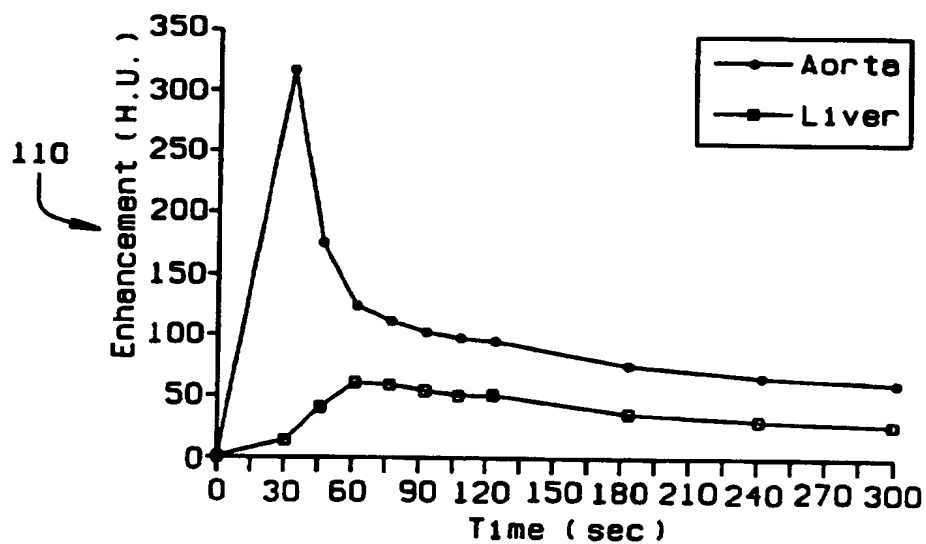


FIG. 12(a)

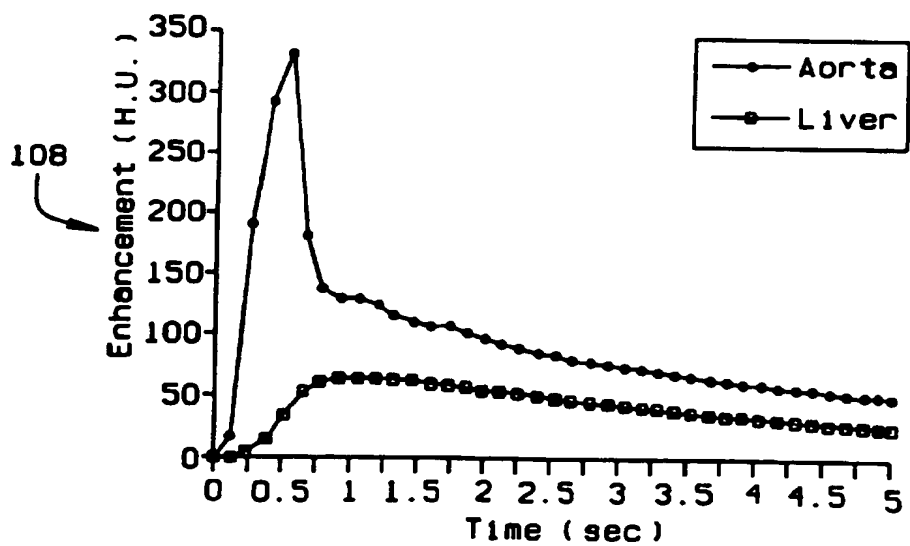


FIG. 12(b)

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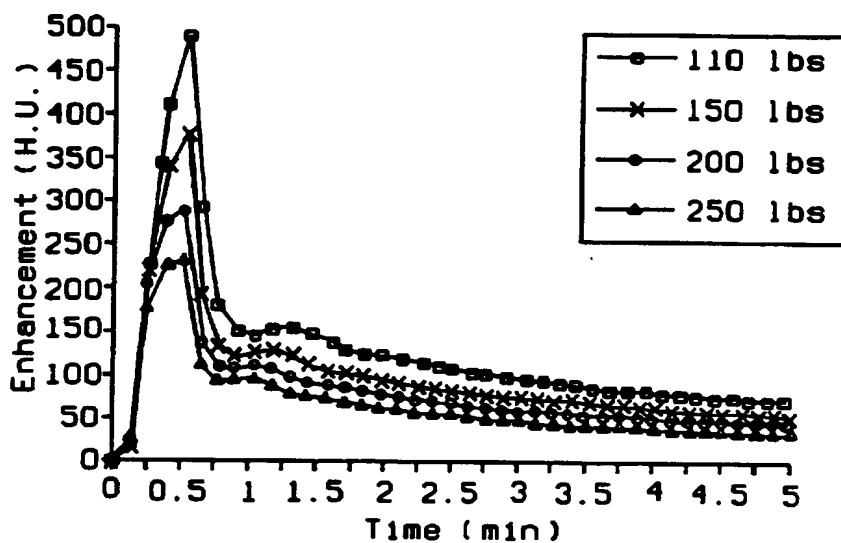


FIG. 13(a)

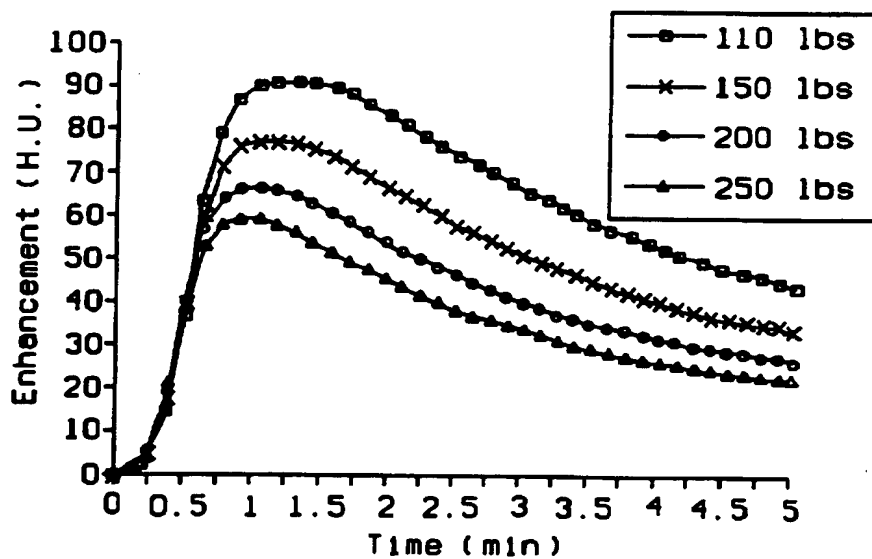


FIG. 13(b)

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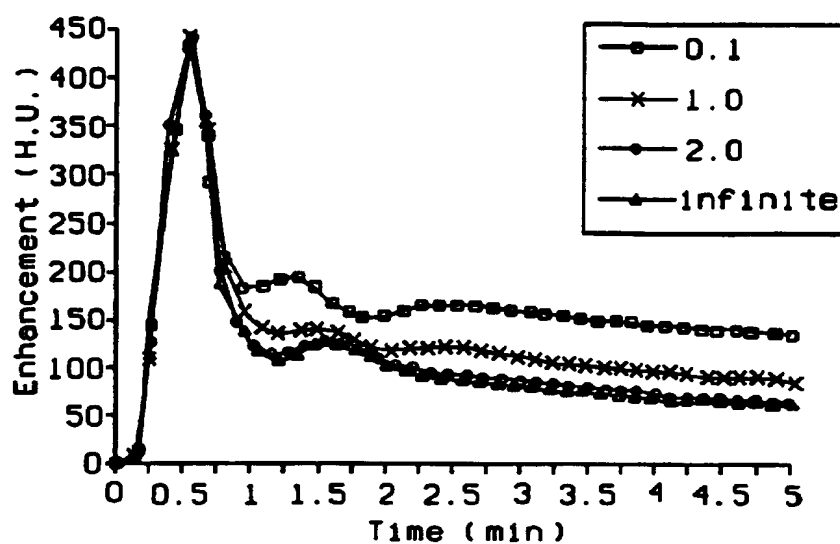


FIG. 14(a)

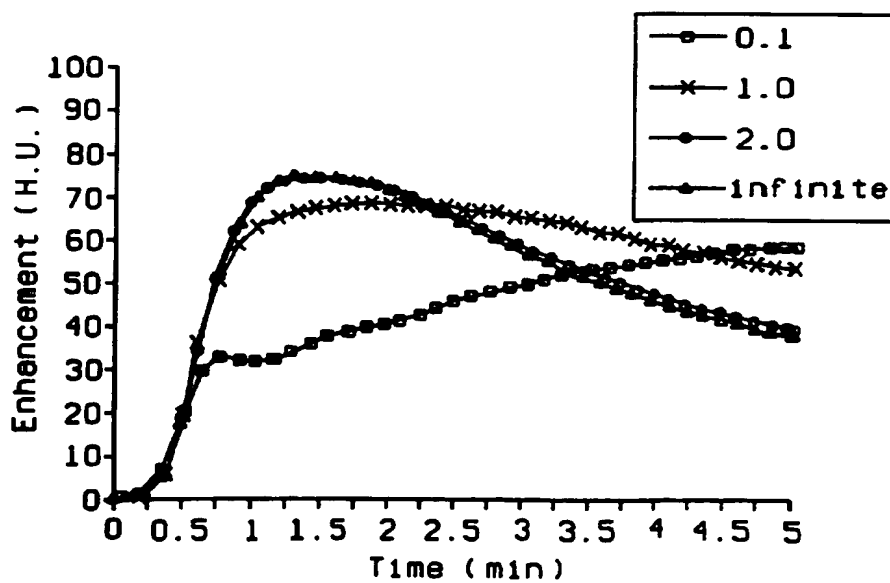


FIG. 14(b)

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Enhancement (H.U.)

TIME (MIN.) AORTIC HEPATIC

| | | |
|------|--------|-------|
| 0 | 0 | 0 |
| 0.13 | 16.23 | 0.02 |
| 0.25 | 187.3 | 3.12 |
| 0.38 | 285.65 | 15.53 |
| 0.51 | 324.22 | 34.8 |
| 0.64 | 176.9 | 52.39 |
| 0.77 | 135.62 | 60.29 |
| 0.91 | 127.09 | 62.9 |
| 1.04 | 127.15 | 63.57 |
| 1.17 | 122.31 | 63.57 |
| 1.3 | 114.23 | 63 |
| 1.43 | 108.87 | 61.84 |
| 1.56 | 106.65 | 60.38 |
| 1.69 | 104.54 | 58.93 |
| 1.82 | 100.87 | 57.47 |
| 1.95 | 96.48 | 56 |
| 2.07 | 92.46 | 54.45 |
| 2.2 | 89.1 | 52.81 |
| 2.34 | 86.21 | 51.15 |
| 2.47 | 83.57 | 49.55 |
| 2.59 | 81.09 | 48.04 |
| 2.73 | 78.65 | 46.51 |
| 2.85 | 76.5 | 45.11 |
| 2.98 | 74.49 | 43.79 |
| 3.11 | 72.56 | 42.51 |
| 3.23 | 70.72 | 41.29 |
| 3.37 | 68.93 | 40.1 |
| 3.49 | 67.25 | 38.97 |
| 3.63 | 65.63 | 37.87 |
| 3.75 | 64.17 | 36.87 |
| 3.88 | 62.78 | 35.93 |
| 4.01 | 61.45 | 35.01 |
| 4.14 | 60.21 | 34.16 |
| 4.27 | 58.99 | 33.32 |
| 4.4 | 57.83 | 32.52 |
| 4.52 | 56.75 | 31.78 |
| 4.65 | 55.75 | 31.1 |
| 4.78 | 54.79 | 30.44 |
| 4.9 | 53.85 | 29.79 |
| 5 | 53.18 | 29.34 |

FIG. 15

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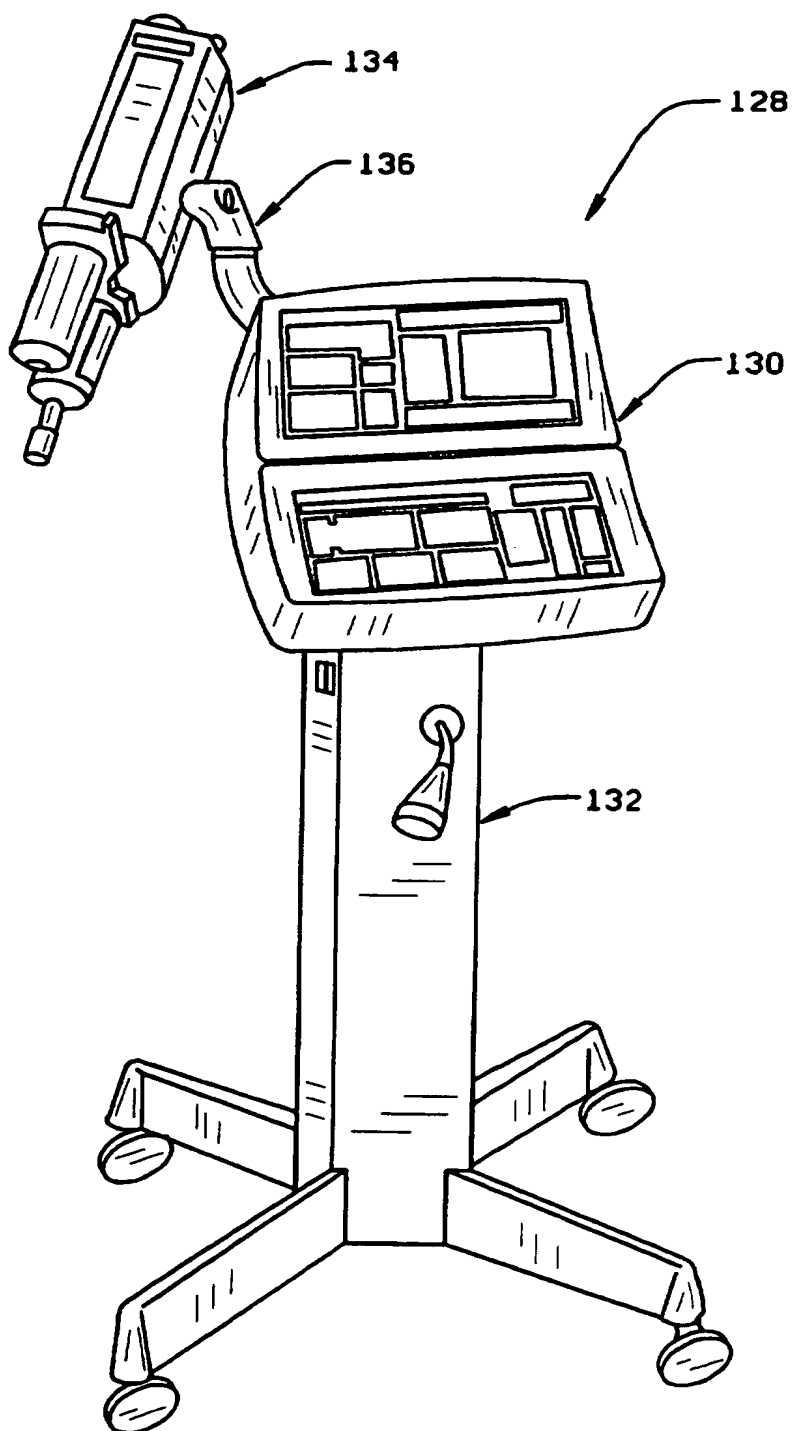
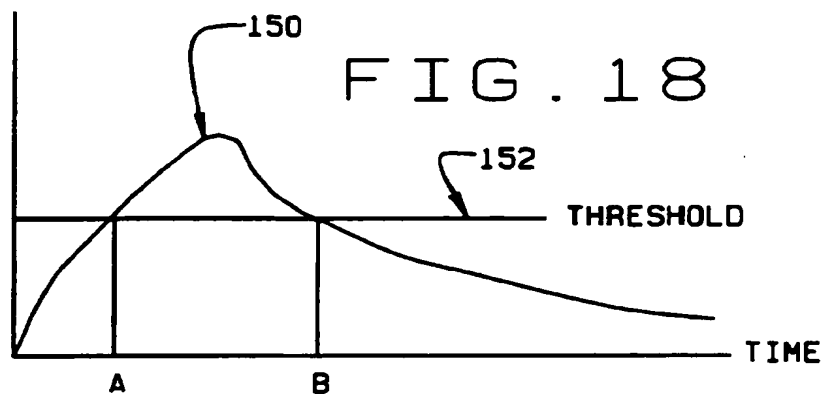


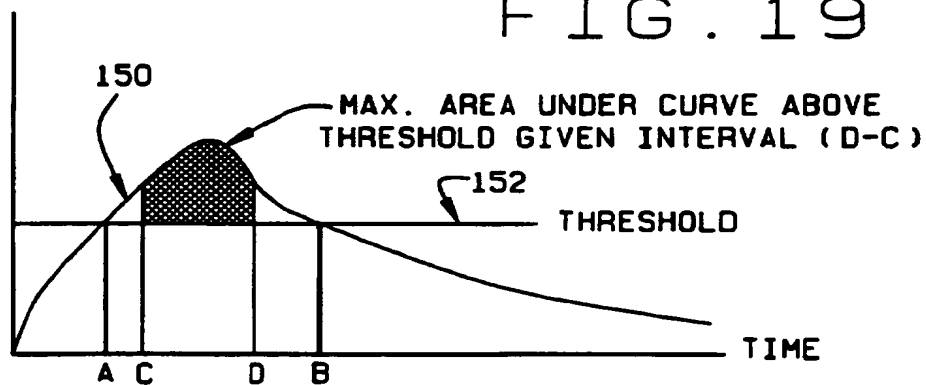
FIG. 17

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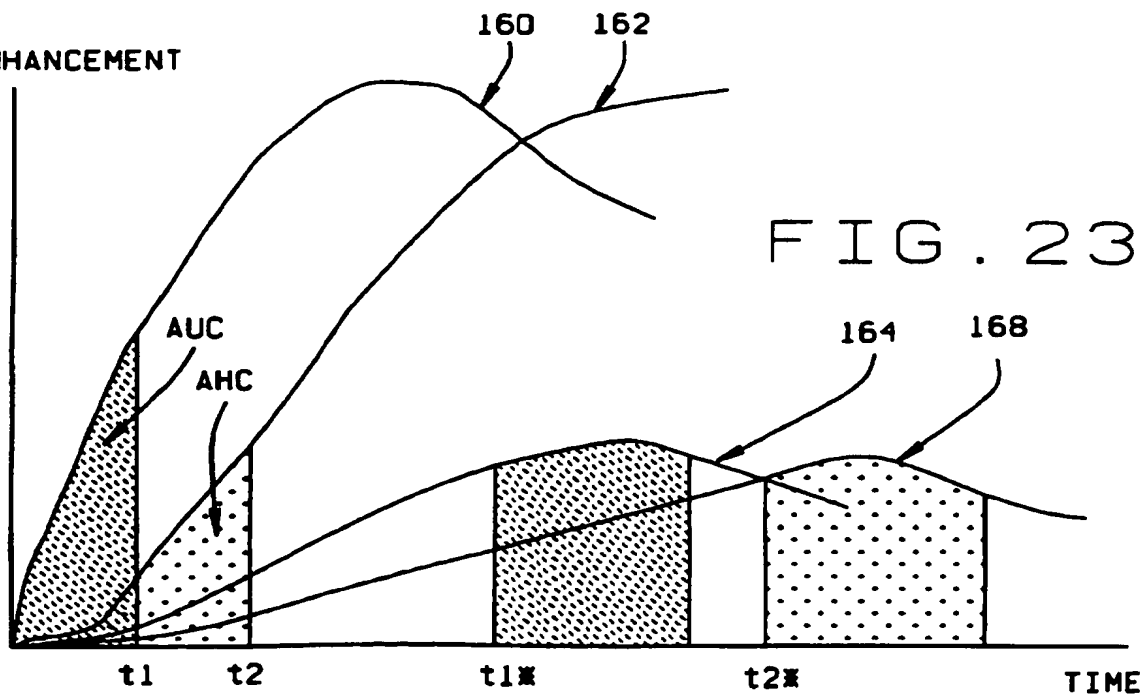
ENHANCEMENT



ENHANCEMENT



ENHANCEMENT



INPUT PARAMETERS 15/20

| | | |
|-----------|-----------------------------------|------------|
| PATIENT | AGE | |
| | GENDER | |
| | HEIGHT | |
| | WEIGHT | |
| | CARDIAC OUTPUT (GOOD, FAIR, POOR) | |
| INJECTION | UNI- vs. BIPHASIC | UNI |
| | VOLUME | 120ml |
| | CONCENTRATION | 300 mg/ml |
| | INJECTION RATE | 3ml/sec |
| CT SCAN | EXAM TYPE (LIVER, VASCULAR) | LIVER |
| | SCAN DURATION | 30 seconds |

OUTPUT PARAMETERS:

PREDICTED CONTRAST ENHANCEMENT CURVE

ENHANCEMENT ADEQUACY (y/n)

SCAN DURATION ABOVE ADEQUACY THRESHOLD

IF NO, INCREASE VOLUME, OR RATE

IF YES, DECREASE VOLUME, OR RATE

OPTIMAL SCAN DELAY

CARDIAC OUTPUT = 100%

| TIME | PREDICTED HEPATIC ENHANCEMENT LEVEL | SUBTRACT THRESHOLD OF ADEQUACY (50 HU) | COMPUTE AREA UNDER CURVE (AUC) OVER SCAN DURATION (30 SECONDS) | OPTIMAL TEMPORAL WINDOW |
|---------|--|---|---|-------------------------------|
| SECONDS | HU | HU | HU*SEC | |
| 0 | 0 | -50 | | |
| 5 | 0 | -50 | | |
| 10 | 0 | -50 | | |
| 15 | 1 | -49 | | |
| 20 | 4 | -46 | | |
| 25 | 10 | -40 | | |
| 30 | 17 | -33 | | |
| 35 | 25 | -25 | | |
| 40 | 34 | -16 | 9.6 | |
| 45 | 43 | -7 | 129.0 | |
| 50 | 49 | -1 | 205.6 | |
| 55 | 53 | 3 | 246.6 | |
| 60 | 56 | 6 | 263.8 | |
| 65 | 58 | 8 | 263.7 | START SCAN |
| 70 | 58 | 8 | 252.6 | |
| 75 | 58 | 8 | 233.9 | |
| 80 | 58 | 8 | 209.8 | |
| 85 | 58 | 8 | 181.9 | |
| 90 | 57 | 7 | 151.4 | END SCAN |
| 95 | 56 | 6 | 119.4 | |
| 100 | 55 | 5 | 86.0 | |
| 105 | 54 | 4 | 51.5 | |

SCAN IS STARTED AT MAXIMUM AUC (263.8 HU*SEC) OVER THE SCAN DURATION
(BOLD = SCAN DURATION)

FIG. 20

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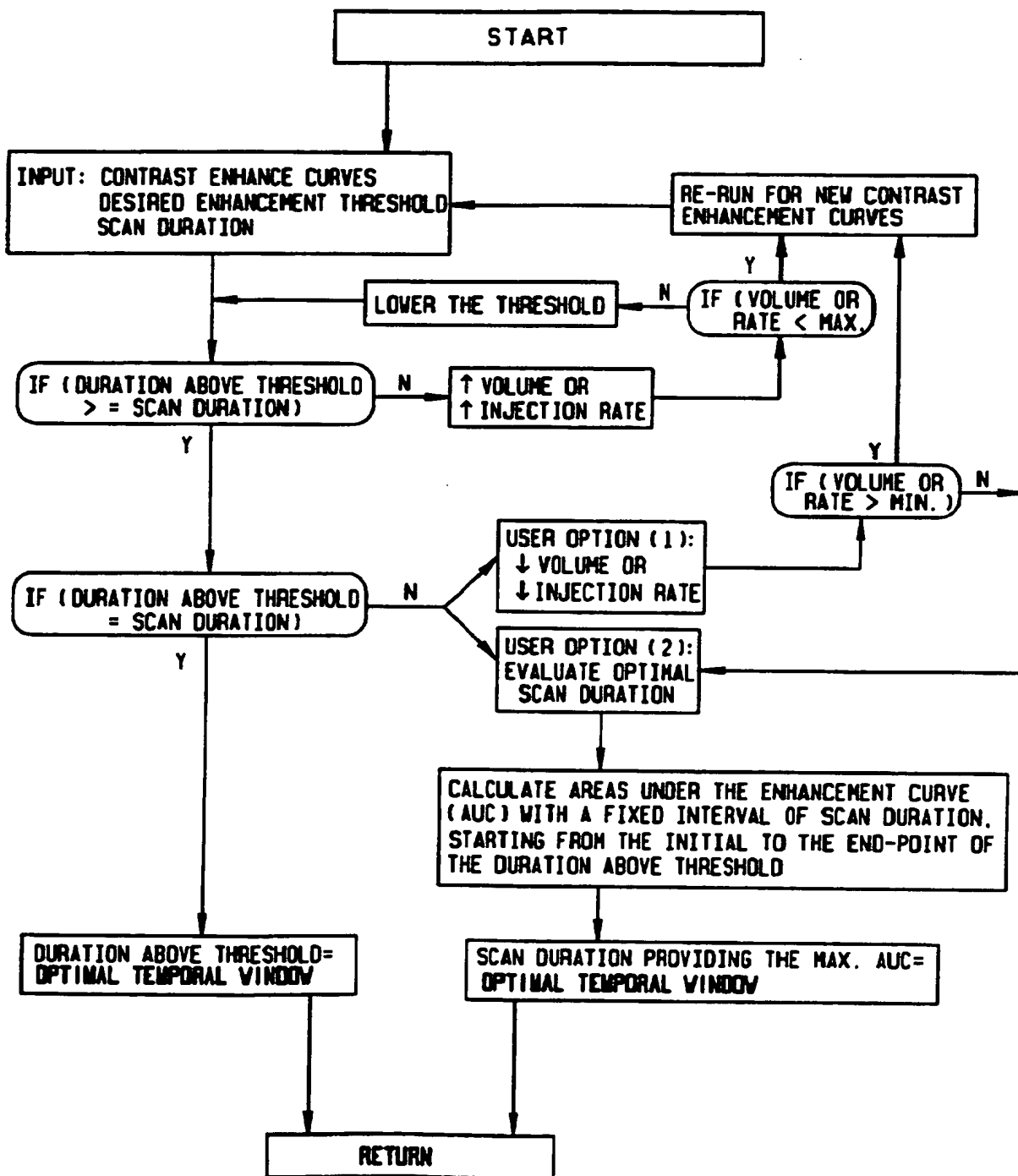


FIG. 21

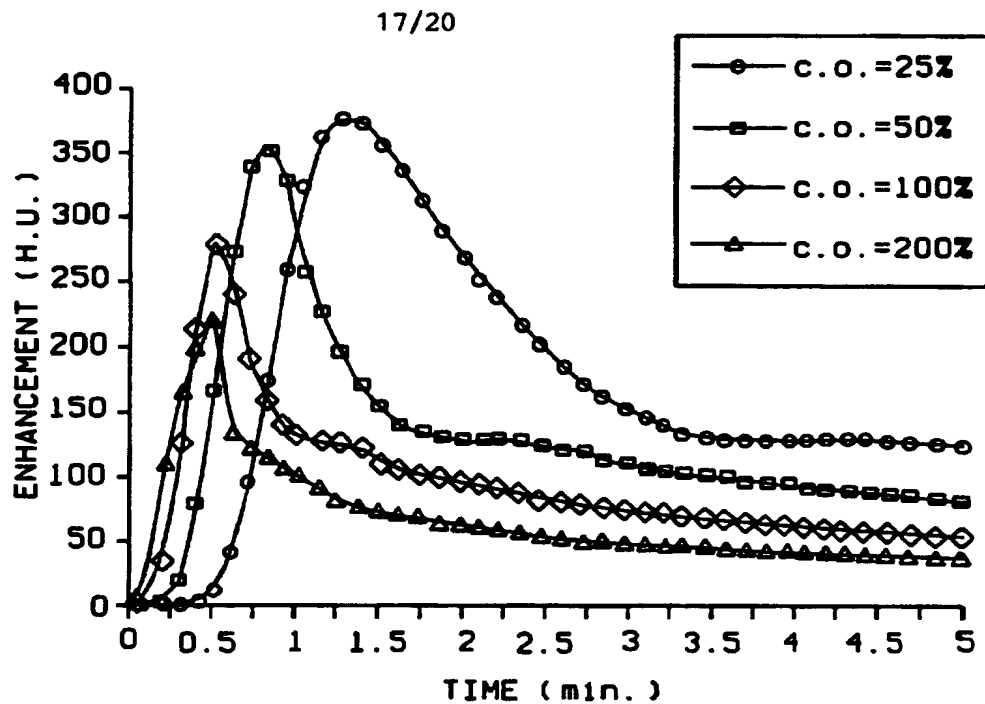


FIG. 22A

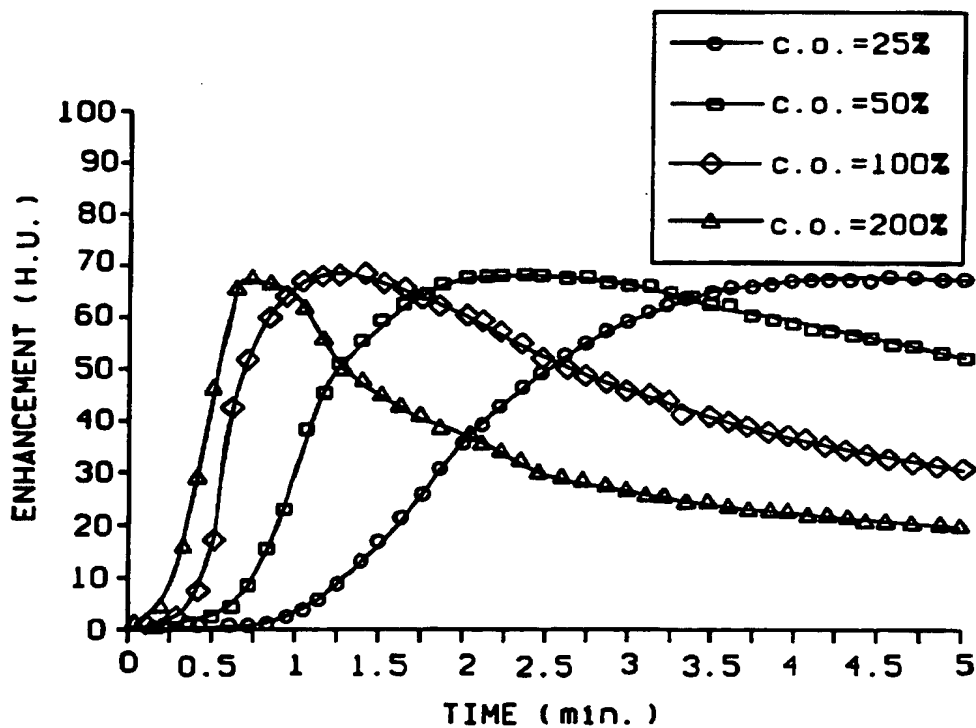


FIG. 22B

| ADJUST OPTIMAL SCAN TIMING WITH CARDIAC VARIATION | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|--|
| CARDIAC OUTPUT=200Z | | | | | CARDIAC OUTPUT=75Z | | | | |
| TIME | PREDICTED AORTIC ENHANCEMENT LEVEL | PREDICTED AORTIC ENHANCEMENT AUC | PREDICTED AORTIC ENHANCEMENT LEVEL | PREDICTED AORTIC ENHANCEMENT AUC | PREDICTED AORTIC ENHANCEMENT LEVEL | PREDICTED AORTIC ENHANCEMENT AUC | PREDICTED AORTIC ENHANCEMENT LEVEL | PREDICTED AORTIC ENHANCEMENT AUC | ACTUAL AORTIC ENHANCEMENT AUC |
| SECONDS | HU | HU•SEC | HU | HU•SEC | HU | HU•SEC | HU | HU•SEC | HU |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 11 | 56 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 10 | 60 | 354 | 22 | 113 | 0 | 37 | 0 | 2 | 39 |
| 15 | 93 | 819 | 72 | 475 | 48 | 275 | 11 | 56 | 273 |
| 20 | 115 | 1391 | 120 | 1074 | 99 | 768 | 45 | 281 | 776 |
| 25 | 134 | 2059 | 158 | 1864 | 148 | 1508 | 95 | 755 | 1527 |
| 30 | 152 | 2819 | 187 | 2801 | 190 | 2459 | 151 | 1509 | 2485 |
| 35 | 169 | 3663 | 212 | 3864 | 225 | 3582 | 200 | 2507 | 3601 |
| 40 | 147 | 4396 | 220 | 4965 | 249 | 4828 | 242 | 3716 | 4841 |
| 45 | 121 | 5003 | 189 | 5912 | 244 | 6047 | 279 | 5109 | 6050 |
| 50 | 110 | 5553 | 159 | 6705 | 210 | 7097 | 287 | 6544 | 7109 |
| 55 | 104 | 6074 | 140 | 7403 | 179 | 7990 | 269 | 7890 | 8007 |
| 60 | 98 | 6565 | 127 | 8039 | 157 | 8774 | 240 | 9092 | 8794 |
| 65 | 93 | 7031 | 120 | 8640 | 142 | 9483 | 206 | 10124 | 9504 |
| 70 | 89 | 7476 | 116 | 9220 | 132 | 10142 | 185 | 11047 | 10159 |
| 75 | 85 | 7902 | 112 | 9781 | 126 | 10770 | 165 | 11872 | 10785 |
| 80 | 81 | 8309 | 109 | 10324 | 122 | 11379 | 151 | 12629 | 11392 |
| 85 | 78 | 8696 | 105 | 10850 | 119 | 10975 | 140 | 13329 | 11984 |
| 90 | 74 | 9068 | 102 | 11362 | 116 | 12556 | 133 | 13992 | 12560 |
| 95 | 72 | 9426 | 100 | 11862 | 113 | 13122 | 128 | 14630 | 13119 |
| 100 | 69 | 9771 | 98 | 12352 | 110 | 13671 | 124 | 15252 | 13662 |
| 105 | 67 | 10104 | 96 | 12831 | 106 | 14202 | 123 | 15866 | 14190 |
| 110 | 64 | 10426 | 94 | 13299 | 104 | 14721 | 122 | 16474 | 14705 |
| 115 | 62 | 10738 | 91 | 13754 | 102 | 15231 | 120 | 17074 | 15211 |
| 120 | 60 | 11040 | 89 | 14197 | 100 | 15733 | 118 | 17665 | 15709 |
| 125 | 59 | 11333 | 86 | 14629 | 99 | 16228 | 116 | 18244 | 16200 |
| 130 | 57 | 11617 | 84 | 15050 | 98 | 16716 | 113 | 18810 | 16685 |
| 135 | 55 | 11894 | 82 | 15460 | 96 | 17197 | 111 | 19364 | 17160 |

ACTUAL AORTIC ENHANCEMENT AUC IS 776 HU•SEC AT 20 SECONDS (BOLD) AND MOST CLOSELY MATCHES PREDICTED AORTIC ENHANCEMENT AUC AT 20 SECONDS (768 HU•SEC) FOR PATIENT WITH CARDIAC OUTPUT OF 75Z. OPTIMAL TEMPORAL WINDOW FOR HEPATIC ENHANCEMENT IS COMPUTED BY ANALYZING PREDICTED HEPATIC ENHANCEMENT CURVE FOR PATIENT WITH CARDIAC OUTPUT OF 75Z (FIG.25).

FIG. 24

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CALCULATION OF THE TEMPORAL WINDOW FOR OPTIMAL ENHANCEMENT

CARDIAC OUTPUT = 75%

| TIME | PREDICTED HEPATIC ENHANCEMENT LEVEL | SUBTRACT THRESHOLD OF ADEQUACY (50 HU) | COMPUTE AREA UNDER CURVE (AUC) OVER SCAN DURATION (30 SECONDS) | OPTIMAL TEMPORAL WINDOW |
|-----------|--|---|---|-------------------------------|
| SECONDS | HU | HU | HU*SEC | |
| 0 | 0 | -50.0 | | |
| 5 | 0 | -50.0 | | |
| 10 | 0 | -50.0 | | |
| 15 | 0 | -49.7 | | |
| 20 | 2 | -48.5 | | |
| 25 | 4 | -45.6 | | |
| 30 | 9 | -40.7 | | |
| 35 | 16 | -34.3 | | |
| 40 | 23 | -27.4 | | |
| 45 | 30 | -19.8 | | |
| 50 | 38 | -11.6 | 23.8 | |
| 55 | 45 | -5.2 | 122.8 | |
| 60 | 49 | -0.5 | 191.0 | |
| 65 | 53 | 2.8 | 236.3 | |
| 70 | 55 | 5.1 | 264.5 | |
| 75 | 57 | 6.6 | 279.2 | |
| 80 | 58 | 7.6 | 284.0 | START SCAN |
| 85 | 58 | 8.2 | 281.3 | |
| 90 | 58 | 8.5 | 272.6 | |
| 95 | 59 | 8.5 | 259.3 | |
| 100 | 58 | 8.4 | 242.1 | |
| 105 | 58 | 8.0 | 222.3 | |
| 110 | 58 | 7.6 | 200.7 | END SCAN |
| 115 | 57 | 7.1 | 177.8 | |
| 120 | 56 | 6.4 | 154.2 | |
| 125 | 56 | 5.8 | 130.1 | |
| 130 | 55 | 5.1 | 105.7 | |
| 135 | 54 | 4.4 | 80.6 | |
| 140 | 54 | 3.7 | 54.8 | |
| 145 | 53 | 3.0 | | |
| 150 | 52 | 2.3 | | |
| 155 | 52 | 1.6 | | |
| 160 | 51 | 0.9 | | |
| 165 | 50 | 0.1 | | |
| 170 | 49 | -0.7 | | |

SCAN IS STARTED AT MAXIMUM AUC (284.0 HU*SEC) OVER THE SCAN DURATION
(BOLD = SCAN DURATION)

FIG. 25

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SUBROUTINE ADJUSTING ONSET OF SCANNING
(INDEPENDENT INJECTOR SYSTEM)

INPUT: PRECIDIOTED WITH STANDARD CARDIAC OUTPUT
AUC1 (AREA UNDER EARLY AORTIC CURVE)
t1 (SCAN DURATION TO ACHIEVE AUC1)
t1x (PREDICTED ONSET OF HEPATIC SCAN)

FOR DIFFERENT LEVELS OF CARDIAC OUTPUT,
CALCULATE A SET OF t1'S YIELDING IDENTICAL
AUC1 AND CORRESPONDING t1x'S

CONSTRUCT AN INTERPOLATING LOOK-UP TABLE
FOR t1x'S AT VARIOUS t1'S

MEASUREMENT FROM LOW-DOSE PRESCAN CT

CALCULATE CUMULATIVE AUC1 (at t1)
AS SCAN PROCEEDS (INCREMENTAL Δt)

IF (AUC1 = AUC1)

N

Y

t1=t1

t2x (UPDATED ONSET OF HEPATIC SCAN)
IS DETERMINED FROM THE LOOK-UP TABLE

RETURN

FIG. 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15680

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 6/03

US CL :378/8, 95; 364/413.15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 378/4, 8, 95, 98.9, 98.11, 98.12, 210, 901; 364/413.14, 413.15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

search terms: contrast agent, computed tomography, patient, parameter, injection, protocol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,034,987 A (FUJIMOTO et al.) 23 July 1991 | All |
| A | US 5,301,672 (KALENDER) 12 April 1994 | All |
| A | US 5,383,231 (YAMAGISHI) 12 January 1995 | All |
| A, P | US 5,459,769 (BROWN) 17 October 1995 | All |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" earlier document published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" document member of the same patent family |
| "O" document referring to an oral disclosure, use, exhibition or other means | |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

09 JANUARY 1997

Date of mailing of the international search report

28 JAN 1997

Name and mailing address of the ISA/US
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Washington, D.C. 20231

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